# Comparison of brain function and structure between paediatric OCD and ADHD patients.

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# Comparison of brain function and structure between paediatric OCD and ADHD patients.

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I dedicate this PhD in loving memory of my dearly missed friend, Baocong Xia (1992-2016).

**Abstract**

This thesis examined whether the neural underpinnings of common deficits in inhibitory control, sustained attention, and decision-making are the same or disorder-specific in ADHD and OCD. It contains a comparative multi-modal meta-analysis of voxel-based morphometry (VBM) studies of grey matter volume and functional magnetic resonance imaging (fMRI) studies of inhibitory control in ADHD and OCD and a fMRI study comparing adolescents with ADHD, adolescents with OCD and healthy control adolescents during (i) sustained attention (ii) temporal discounting and (iii) gambling.

The meta-analysis showed disorder-specific functional and structural abnormalities in basal ganglia and insula, which were reduced in ADHD but increased in OCD relative to controls, and in frontal regions, where rostro-dorsal medial frontal regions were disorder-specifically decreased in structure and function in OCD, but where inferior lateral prefrontal regions were disorder-specifically underactive in ADHD.

During sustained attention, patients showed disorder-specific abnormalities in task-relevant and default mode networks. ADHD patients showed disorder-specific lateral prefrontal while OCD patients showed disorder-specific medial frontal deficits. In the default mode network, patients with OCD showed disorder-specific abnormalities in ventromedial and patients with ADHD in rostromedial regions.

During temporal discounting, both patient groups shared underactivation in fronto-striato-insular-cerebellar regions responsible for self-control and temporal foresight, suggesting that choice impulsivity is mediated by largely shared neural dysfunctions in both disorders. OCD patients showed disorder-exclusive dysfunction in orbitofrontal and rostrolateral prefrontal cortex.

During a gambling task, patients with ADHD and OCD showed shared underactivation in the ventral striatum during advantageous choices, but OCD patients showed disorder-specific underactivation in ventromedial orbitofrontal cortex. Patient groups shared underactivation in medial prefrontal cortex to loss outcomes, and in putamen and precueus to wins, relative to controls.

In conclusion, findings suggest partially shared but largely disorder-specific neural dysfunction during in ADHD and OCD.

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**List of abbreviations used throughout the thesis (in order of appearance)**

**ADHD:** Attention-Deficit/Hyperactivity Disorder.

**DSM-5**: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition.

**OCD**: Obsessive/compulsive disorder.

**SSRI:** Serotonin re-uptake inhibitor.

**CBT**: cognitive behavioural therapy.

**ERP:** exposure and response prevention.

**DMN**: default mode network.

**EF:** Executive function.

**SSRT:** Stop Signal Reaction Time.

**WCST:** Wisconsin Card Sorting Test.

**ID/ED:** intra-dimensional/extra-dimensional set-shifting task.

**CPT:** Continuous Performance Task.

**SART:** Sustained Attention to Response Task.

**TD:** temporal discounting.

**CGT**: Cambridge Gambling Task

**GDT:** Game of Dice Task.

**IGT:** Iowa gambling task.

**vmOFC:** ventromedial orbitofrontal cortex.

**sMRI:** Structural Magnetic Resonance Imaging**.**

**ROI:** Region of Interest.

**WMV:** White Matter Volume.

**GMV:** Grey Matter Volume.

**fMRI:** Functional Magnetic Resonance Imaging.

**EEG:** Electroencephalography.

**ERP:** Event-Related Potentials.

**fNIRS**: Functional Near-Infrared Spectroscopy.

**PET:** Positron Emission Tomography.

**VBM:** Voxel-Based Morphometry.

**IFG:** Inferior Frontal Gyrus.

**r/d:** Rostral/Dorsal.

**MPFC:** Medial Prefrontal Cortex.

**ACC:** Anterior Cingulate Cortex.

**OFC:** Orbitofrontal Cortex.

**DLPFC:** Dorsolateral Prefrontal Cortex.

**PCC:** Posterior Cingulate Cortex.

**mACC:** Middle Anterior Cingulate Cortex.

**SMA:** Supplementary Motor Area.

**VS:** Ventral Striatum.

**MID:** Monetary Incentive Delay.

**AES-SDM**: Anisotropic Effect-Size Seed-based d Mapping.

**WASI-R**: Wechsler Abbreviated Scale of Intelligence-Revised.

**DSM-IV:** Diagnostic and Statistical Manual of Mental Disorders Fourth Edition.

**CPRS-R:** Conner's Parent Rating Scale-Revised.

**SDQ:** Strength and Difficulty Questionnaire.

**ICD-10:** 10th edition of the International Classification of Diseases.

**CY-BOCS:** Children's Yale-Brown Obsessive Compulsive Scale.

**SAT:** sustained attention task.

**CEN:** central executive network.

**VAN:** ventral attention network.

**SN:** salience network.

**mACC**: middle anterior cingulate cortex.

**dACC:** dorsal anterior cingulate cortex.

**A/VMPFC:** anterior/ventromedial prefrontal cortex.

**RLPFC:** rostrolateral prefrontal cortex.

# Chapter 1. Background on Attention-Deficit/Hyperactivity Disorder and Obsessive/compulsive disorder

## 1.1. Attention-Deficit/Hyperactivity Disorder

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common developmental psychiatric disorder which affects around 5-10% of children (Froehlich et al., 2007; Polanczyk & Rohde, 2007; Thomas, Sanders, Doust, Beller, & Glasziou, 2015; Willcutt, 2012) and 2-5% of adults (de Zwaan et al., 2012; Faraone & Biederman, 2005; Faraone, Sergeant, Gillberg, & Biederman, 2003; Kessler et al., 2006; Simon, Czobor, Balint, Meszaros, & Bitter, 2009), that has a significant negative impact on mental health, family functioning, and educational attainment (Barkley, 2002; Klein et al., 2012). In Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), ADHD is as categorised as a childhood-onset neurodevelopmental disorder, with the symptoms being age inappropriate inattention and impulsivity/hyperactivity. ADHD symptoms must be observable in more than one context (e.g., home, school) and have been present prior to age 12 years. There are three symptom subtypes, which include ADHD-inattentive subtype, ADHD-hyperactive/impulsive subtype, and ADHD-combined subtype. The combined subtype is the most commonly diagnosed (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Although traditionally considered a disorder of childhood, impairing levels of symptoms most often persist into adulthood, with complete remission reported in only 20% of childhood cases (Biederman, Mick, & Faraone, 2000; Du Rietz et al., 2016; Faraone, Biederman, & Mick, 2006). Research recent has also suggested the existence of adult onset ADHD (Moffitt et al., 2015).

The current first line treatments for ADHD are psychostimulants, including methylphenidate and amphetamines, which reduce ADHD core symptoms in about 70% of patients, and meta-analyses report large effect sizes for the efficacy of psychostimulants in ADHD relative to

placebo (Chan, Fogler, & Hammerness, 2016; Faraone, 2009; Faraone & Buitelaar, 2010). Atomoxetine, a selective presynaptic norepinephrine transporter blocker, is a second line treatment with similar efficacy to psychostimulants in treating ADHD, although it takes six to eight weeks to start producing an equivalent reduction in symptoms (Bushe & Savill, 2014; Chan et al., 2016).

Adoption studies show that only biological relatives of ADHD patients are at increased risk for the disorder, supporting a primarily genetic model of familial risk for ADHD (Larsson, Chang, D'Onofrio, & Lichtenstein, 2014). Twin studies suggest heritability estimates of 60-80% for ADHD, whether based on continuous ratings of ADHD symptoms in population samples or on disorder diagnosis (Larsson et al., 2014; Nikolas & Burt, 2010). Around 25% of the aetiology is explained by non-shared environmental factors, and only 1% is explained by shared environmental factors (Faraone et al., 2005).

### 1.2 Obsessive/compulsive disorder

Obsessive/compulsive disorder (OCD) is characterized by two primary symptom dimensions. The first of these is obsessions, which are unwanted, intrusive, and recurrent thoughts often revolving around the themes of contamination, checking, orderliness and symmetry. These are typically accompanied by behavioural and mental rituals (compulsions) which are performed to relieve distress, such as repetitive washing, checking, and the reordering of items. DSM-5 diagnostic criteria requires that obsessions or compulsions are time consuming and cause distress or have a significant impact on daily functioning (American Psychiatric Association, 2013). In DSM-5, OCD is classified within the Obsessive/compulsive and Related Disorders chapter along with Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania, and Excoriation Disorder (American Psychiatric Association, 2013).

OCD has a severe impact on reported quality of life, and has a negative impact on education, occupational performance and interpersonal relationships (Huppert, Simpson, Nissenson, Liebowitz, & Foa, 2009; Stengler-Wenzke, Kroll, Matschinger, & Angermeyer, 2006; Storch, Abramowitz, & Keeley, 2009). The disorder affects around 2.3% of adults (Ruscio, Stein, Chiu, & Kessler, 2010) and 1-3% of children and adolescents (Canals, Hernandez-Martinez, Cosi, & Voltas, 2012; Rapoport et al., 2000). Around 30-50% of OCD patients experience onset before the age of 18, and paediatric cases persist into adulthood in 40% of cases (Micali et al., 2010; Stewart et al., 2004). Age of onset appears to follow a bimodal distribution, with peaks at around 10 and 20 years of age (Delorme et al., 2005; Kessler et al., 2005; Ruscio et al., 2010). Childhood onset OCD may represent a distinct disorder subtype, as it is associated with greater comorbidities, greater familial influence, male preponderance, and poorer insight (Delorme et al., 2005; Geller et al., 1998; Ruscio et al., 2010).

Serotonin re-uptake inhibitor (SSRIs) including citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline and the non-selective re-uptake inhibitor clomipramine are the first line pharmacological treatment for OCD, which have been shown to be more effective than placebo with a medium effect size in meta-analyses of randomized controlled trials in both adult and paediatric patients, although clomipramine is associated with significantly more side-effects than SSRIs (Abramowitz, Whiteside, & Deacon, 2005; Soomro, Altman, Rajagopal, & Oakley Browne, 2008). Around 30% of OCD patients receive augmentation therapy with atypical antipsychotics, including risperidone, quetiapine, olanzapine (Van Ameringen et al., 2014), which have a medium to large effect size as an adjunct therapy when compared with placebo (Dold, Aigner, Lanzenberger, & Kasper, 2015).

Psychological treatments for OCD primarily consist of cognitive behavioural therapy (CBT) incorporating in-vivo exposure and response prevention (ERP). Cognitive therapy is aimed at modifying distorted OCD beliefs, while in ERP patients are required to approach symptom

provoking stimuli while preventing compulsive rituals, therefore reducing anxiety via habituation and learning that compulsive rituals are not required to prevent feared outcomes or reduce anxiety. CBT is associated with a medium to large effect sizes in reducing symptoms in adult and paediatric OCD (Abramowitz et al., 2005; Ost, Havnen, Hansen, & Kvale, 2015).

There is evidence for a genetic component to OCD. Family studies show that first degree relatives of OCD probands are 4-5 times more likely to have OCD than the general population, while second and third degree relatives are, respectively, 2 and 1.5 times more likely to have OCD (Mataix-Cols et al., 2013; Taylor, 2011). Twin studies based on population samples suggest heritability rates of 30–40% (Taylor, 2011). Environmental risk factors are primarily non-shared (~50%) while contributions from shared environment factors are small (5-6%) (Taylor, 2011).

### 1.3. OCD and ADHD: comorbidities and similarities.

Despite their distinct symptoms profiles, ADHD and OCD show a high degree of comorbidity (Brown, Katz, Roth, & Beers, 2014; Geller et al., 2007a). In OCD youth, estimates vary between 0% and 60% comorbidity with ADHD, although in 17 out of 29 published studies comorbidity estimates were above 20% (Tan, Metin, & Metin, 2016). In ADHD youth, estimates of OCD comorbidity are more modest (0-7.5%) (Abramovitch, Dar, Mittelman, & Wilhelm, 2015; Tan et al., 2016). The majority of these studies have used clinical samples, and comorbidity may be overestimated as more complex comorbid patients may be more likely to seek treatment (Abramovitch, Dar, et al., 2015). However, a population study of US adolescent military recruits found that 8 % of ADHD adolescents met criteria for OCD, while 9% of OCD adolescents met criteria for ADHD (Zohar et al., 1992). In adults, the US National Comorbidity Survey reported that ADHD was present in 19% of patients

meeting criteria for OCD (Ruscio et al., 2010), although interestingly adult patients with ADHD did not show significantly heightened OCD comorbidity (Kessler et al., 2006). A family study of patients with Tourette Syndrome found significant genetic correlation between ADHD and OCD, with offspring of mothers with ADHD 1.85 times more likely to meet diagnostic criteria for OCD than children of mothers without ADHD (Mathews & Grados, 2011). A recent study of a large population-representative sample of Swedish adult twins found that ADHD and OCD showed moderate but significant covariation, suggestive of a partially shared genetic basis (Pinto et al., 2016).

Family studies by Geller and colleagues suggest that OCD and ADHD may co-segregate in families. In a study of 1057 first-degree relatives of three groups of children (OCD+ADHD, OCD-ADHD, OCD and ADHD free), relatives meeting criteria for ADHD also had a significantly elevated risk for OCD compared to relatives unaffected by ADHD (20% vs. 4.9%) (Geller et al., 2007b). Similarly, in a study of 1533 first-degree relatives of three groups of children (ADHD+OCD, ADHD-OCD, ADHD and OCD free), relatives with ADHD had a significantly increased risk for OCD compared with relatives without ADHD (7.4% vs. 1.3%) (Geller et al., 2007a).

In early models, ADHD and OCD were characterized as archetypal disorders of impulsivity and compulsivity respectively, and placed at opposing ends of a hypothesized impulsivity-compulsivity spectrum (Fineberg et al., 2014; Robbins, Gillan, Smith, de Wit, & Ersche, 2012). However, the high levels of comorbidity between these two disorders does not fit with this model, and instead point to the potential for an overlap in genetic and neuroendophenotypic features in order to explain their common co-occurrence (Fineberg et al., 2014; Robbins et al., 2012).

Both disorders have deficits in inhibitory control, which may underlie problems with impulsivity in ADHD, and poor control over intrusive obsessive thoughts and compulsions in OCD (Barkley, 1997; Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; Fineberg et al., 2014; Robbins et al., 2012).

ADHD and OCD are also hypothesised to share an imbalance between task-positive brain networks important for maintaining exteroceptive attention and performing goal-directed behaviours, and the default mode network (DMN), which is proposed to mediate internally generated often goal-irrelevant cognitions such as mind-wandering and rumination, and which often needs to be deactivated during cognitive tasks (Fassbender et al., 2009; Liddle et al., 2011; Metin et al., 2015; Peterson et al., 2009; Raichle, 2015; Sonuga-Barke & Castellanos, 2007; Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012; Stern et al., 2011; Stern et al., 2013). These perturbations in the interplay of task-positive and task-negative brain networks likely underlie shared deficits in sustained attention, and, in particular, poor concentration in ADHD (Huang-Pollock, Karalunas, Tam, & Moore, 2012), and difficulties disengaging from obsessional thoughts in OCD (Clayton, Richards, & Edwards, 1999; Seli, Risko, Purdon, & Smilek, 2016; Stern et al., in press).

Both patient groups are also proposed to be associated with choice impulsivity, with impulsive decision-making a key clinical feature of ADHD (Jackson & MacKillop, 2016; Noreika, Falter, & Rubia, 2013), while in OCD choice impulsivity is potentially manifested as a tendency to perform behavioural rituals in order to bring about an initially rewarding outcome (i.e., relieve anxiety) despite negative long-term consequences (Cavedini et al., 2002; Grassi et al., 2015; Sohn, Kang, Namkoong, & Kim, 2014).

In addition, both ADHD and OCD appear to have impairments in learning and utilising behaviour-outcome contingencies to guide goal-directed behaviour, with this proposed to

underlie respective impulsive and compulsive behaviours in ADHD and OCD (Gillan & Robbins, 2014; Tripp & Wickens, 2008; Tripp & Wickens, 2009), and both disorders show impaired decision-making as well as structural and functional abnormalities in underlying orbito-striato-limbic brain regions (Groen, Gaastra, Lewis-Evans, & Tucha, 2013; Jackson & MacKillop, 2016; Plichta & Scheres, 2014; Radua & Mataix-Cols, 2009; Radua, van den Heuvel, Surguladze, & Mataix-Cols, 2010; Remijnse, Nielen, van Balkom, et al., 2006; Sohn et al., 2014).

However, despite these similarities there are also fundamental differences between ADHD and OCD. First, although ADHD and OCD share an overlapping genetic basis, the majority of the genetic variance seems to be disorder-specific, rather than shared between ADHD and OCD, therefore showing that these disorders are not alternative phenotypic expressions of the same underlying genetic liability (Pinto et al., 2016). Moreover, the symptoms of ADHD and OCD are distinct, with ADHD characterized by age inappropriate inattention and impulsivity/hyperactivity, and OCD characterised by obsessions and compulsions, and the associated profiles of ADHD and OCD can in many ways be considered contrasting, with ADHD associated with impulsivity, risky behaviours, while OCD patients are compulsive, risk averse, and harm avoidant (Abramovitch, 2016; Abramovitch, Dar, Hermesh, & Schweiger, 2012; Abramovitch, Dar, et al., 2015). This suggests a strong likelihood of distinctive underlying neurobiology in the pathophysiology of ADHD and OCD, despite surface similarities in neuropsychological and neurofunctional deficits.

## Chapter 2. Executive functions in ADHD and OCD

Executive functions (EFs) can be defined as the higher-order cognitive functions relating to control of thought, action, and emotion, which are necessary for goal-directed behaviour (Stuss & Alexander, 2000). EF can be divided into cool EF and hot EF, where cool EF refers to cognitive processes such as inhibitory control, sustained attention, planning, and working memory, i.e. processes involving abstract and de-contextualized problems with little emotional salience, whereas hot EF refers to processes such as emotional learning, reward-related decision-making, motivated responding, emotion regulation and emotion interference resolution, i.e. processes which involving goal-related utilization or regulation of emotion and motivation (Hobson, Scott, & Rubia, 2011; Rubia, Halari, Cubillo, et al., 2009a; Zelazo & Carlson, 2012). Due to the focus of this PhD, research in ADHD and OCD in the EF domains of inhibitory control, sustained attention and reward-related decision-making are reviewed in detail below. Research in other EF domains will be reviewed briefly for completeness.

### 2.1. Inhibitory control

Inhibitory control refers to 'the suppression of inappropriate responses, stimulus-response mappings or task-sets' (Aron, Robbins, & Poldrack, 2004, p 174) and is a key executive function supporting goal-directed behaviour (Aron, 2011; Aron, Robbins, & Poldrack, 2004, 2014). Deficits in inhibitory control have been reported across numerous psychiatric disorders, including ADHD and OCD, where they are used to explain the poorly regulated impulsive and compulsive behaviours that, respectively, characterize these disorders (Lipszyc & Schachar, 2010). Inhibitory control is measured in response inhibition, interference inhibition and switching tasks (Aron, 2011; Aron et al., 2004; Smith, Taylor, Brammer, Toone, & Rubia, 2006).

### 2.1.1. Response inhibition

Response inhibition involves the ability to withhold a motor response prior to its initiation or to cancel a response after it has been initiated (Aron, 2011; Aron et al., 2004; Sebastian et al., 2012). It is measured using two primary tasks. In Go/No-Go tasks, participants are instructed to respond to Go cues as quickly as possible, but to refrain from responding to No-Go cues. Go cues make up the majority of trials (typically >70%) creating a prepotent tendency to respond. The primary outcome measure is the number of commission errors during No-Go trials, which reflect difficulties in preventing inappropriate behavioural responses (Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014). In the Stop task (Logan, Schachar, & Tannock, 1997), participants again make speeded responses on the majority of trials to a Go stimulus. However, on a minority of trials presentation of the Go cue is shortly followed by a stop-signal, instructing participants to cancel their response to the current trial. The delay between the presentation of the go stimulus and the presentation of the stop stimulus is dynamically adjusted after each stop trial to ensure that every subject inhibits in 50% of the trials. Performance is modelled as a race between a go process initiated by the go stimulus, and a stop process initiated by the stop signal. When the go processes finishes before the stop process, the response is produced. The response is inhibited when the stop process finishes before the go process (Logan, Cowan, & Davis, 1984; Verbruggen & Logan, 2008). The primary outcome measure is the Stop Signal Reaction Time (SSRT), which is calculated by subtracting the average delay between go- and stop-signal required for a participant to successfully inhibit responses on 50% of stop trials (mean stop-signal delay, SSD) from the mean reaction time to go trials. Longer SSRT indicates poorer inhibitory control (Logan et al., 1984; Verbruggen & Logan, 2008). Across individuals, performance on Go/No-Go and Stop tasks shows a strong significant correlation, further supporting that both measures tap

into shared underlying cognitive constructs (Schachar, Forget-Dubois, Dionne, Boivin, & Robaey, 2011).

### 2.1.2. Interference inhibition

Interference inhibition is the ability to ignore stimulus features that would otherwise interfere with the processing of relevant information (Nee, Wager, & Jonides, 2007). Typically, participants must override a prepotent response tendency towards predominant compatible cues for action that interfere with the goal-directed action (Smith et al., 2006). Relevant tasks include the Stroop Color and Word task (Golden, 1976; Stroop, 1935) the Simon task (Rubia et al., 2006; Simon & Berbaum, 1990), and the Erikson Flanker task (Eriksen & Schultz, 1979).

In the Stroop Color and Word task (Golden, 1976; Stroop, 1935), participants are shown the names of colours written in incongruent ink colours and asked to name the colour of the ink as quickly and as accurately as possible. Accuracy and reaction times are compared with two control conditions. In the word task condition, participants read colour words which are written in black ink. In the colour naming condition, participants name the ink colour of a bar of Xs. In the Stroop condition, interference inhibition is required to overcome the dominant response tendency to read the words.

In the Simon task (Rubia et al., 2006; Simon & Berbaum, 1990), participants are presented with arrows which point in either a leftward or rightward direction. The task requires participants to respond with a left key to left facing arrows and a right key to right facing arrows. In the congruent control condition, left facing arrows are presented on the left side of the screen and right facing on the right side of the screen. In a minority of trials (~10-15%), arrows appear on the incongruent side of where they point. On these trials, participants must

use interference inhibition to prevent responding according to the predominant spatial information while continuing to respond according to arrow direction.

In flanker tasks, participants are instructed to attend to a central arrow, and press a left key when it is facing left and a right key when it is facing right. Four flanker arrows are presented simultaneously on screen. These may point in the same direction as the central arrow (congruent condition) or in the opposing direction to the central arrow (incongruent condition) (Eriksen & Schultz, 1979).

### 2.1.3. Cognitive switching

In cognitive switching tasks, participants must alter their responses to task stimuli flexibly over the course of the task. Inhibitory control is required to inhibit previously valid stimulus-response associations (Aron et al., 2004; Monsell, 2003; Smith, Taylor, Brammer, & Rubia, 2004).

In the Wisconsin Card Sorting Test (WCST), participants learn to classify sort cards based on colour, shape or number. After a string of consecutive correct responses the sorting rule is changed, and participants must inhibit classifications based on the no longer relevant stimulus dimension (perseveration errors) and flexibly shift attentional focus or cognitive set so that responses can be made according to the now correct criterion (Heaton, 1993).

In the intra-dimensional/extra-dimensional set-shifting task (ID/ED), two dimensions are used in the test. These are colour-filled shapes and white lines. In the initial stage of the task (the simple discrimination stage), participants are initially presented with two colour filled shapes and learn to respond according to a stimulus-reward contingency based on task-feedback. In the second stage (simple reversal stage), the outcome contingencies are switched such that previously correct response becomes incorrect. In the third and fourth stages (the

compound discrimination stages), the second stimulus dimension (white lines) is added and presented either side by side with the shape stimuli (third stage) or superimposed on the shape stimuli (fourth stage). Participants must ignore the white lines and continue responding according to the shape dimension. In the intra-dimensional shift stage, novel exemplars of the shape and line stimuli are presented but participants must continue to respond according to the shape dimension. In the extra-dimensional shift stage, novel exemplars of the shape and line stimuli are again presented but participants must now respond according to the line dimension. The intra-dimensional and extra-dimensional shift stages also contain reversal-learning trials, in which the previously correct response becomes incorrect (Downes et al., 1989; Sahakian & Owen, 1992).

Cued task-switching tasks provide a further measure of cognitive switching (Monsell, 2003; Smith et al., 2004). In these tasks, rather than using feedback to initiate switching as in the WCST and ID/ED, explicit cues are presented to participants indicating the task that needs to be performed on the presented stimuli. Responses are slower and more errors are made when participants switch tasks compared with when they repeat the same task on subsequent trials (the switch cost). This results from task-set inertia, which is an interference effect of the previously correct stimulus response links or task set on responses made after a switch, and which must be inhibited for task-switching to be performed (Monsell, 2003; Smith et al., 2004; Wylie & Allport, 2000).

### 2.1.4. Inhibitory control in ADHD

Inhibitory control is purported to be the primary cognitive deficit in ADHD, which is proposed to underlie deficits in controlling impulsive or task-irrelevant thoughts and behaviours (Barkley, 1997; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Wodka et al., 2007).

In Stop tasks, increased SSRT in ADHD patients relative to controls has been reported in a large number of studies (de Zeeuw et al., 2008; Lee et al., 2008; Luman et al., 2009; Martel, Nikolas, & Nigg, 2007; Rommelse et al., 2008; Rubia, Oosterlaan, Sergeant, Brandeis, & v Leeuwen, 1998; Rubia, Smith, & Taylor, 2007; Sebastian et al., 2012), as confirmed in multiple meta-analyses reporting medium effect sizes (Alderson, Rapport, & Kofler, 2007; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Lipszyc & Schachar, 2010; Oosterlaan, Logan, & Sergeant, 1998), providing strong evidence for impaired response cancelation. A large number of studies also report increased commission errors in Go/No-go tasks (Rubia, Smith, & Taylor, 2007; Slaats-Willemse, Swaab-Barneveld, de Sonneville, van der Meulen, & Buitelaar, 2003; Wodka et al., 2007), suggestive of response prevention impairments in ADHD. This finding was recently confirmed in a meta-analyses of 78 studies which reported a medium effect size for increased commission errors in ADHD relative to controls (Wright et al., 2014).

In addition to significant impairment during stop and no-go trials, ADHD patients also show reliably increased reaction times, reaction time variability and omission errors during go trials (Alderson et al., 2007; Kofler et al., 2013; Lijffijt et al., 2005; Wright et al., 2014), which are interpreted as reflecting poor response preparation and lapses in attention to task (Wright et al., 2014).

ADHD patients show increased interference effects during Stroop (Barkley, Grodzinsky, & DuPaul, 1992; Berlin, Bohlin, Nyberg, & Janols, 2004; King, Colla, Brass, Heuser, & von Cramon, 2007; Medrano, Flores-Lazaro, & Nicolini, 2015; Mor, Yitzhaki-Amsalem, & Prior, 2015; Seidman, Biederman, Faraone, Weber, & Ouellette, 1997; Yang et al., 2011; Yasumura et al., 2014), Simon (Cao et al., 2013; Mullane, Corkum, Klein, & McLaughlin, 2009; Sebastian et al., 2012; Suarez et al., 2015) and flanker tasks (Breitling et al., 2016; Crone, Jennings, & van der Molen, 2003). Although negative findings have also been reported

(Adolfsdottir, Sorensen, & Lundervold, 2008; Rubia, Smith, & Taylor, 2007; Rubia, Smith, Brammer, & Taylor, 2007; van Mourik et al., 2009), meta-analyses support increased error rates and reaction times during interference inhibition in ADHD (Homack & Riccio, 2004; Lansbergen, Kenemans, & van Engeland, 2007; Mullane et al., 2009). Stroop interference effect has also been found to correlate with ADHD symptoms in typically developing children (Ikeda, Okuzumi, & Kokubun, 2013).

Patients with ADHD show more perseveration errors during WCST (Dobson-Patterson, O'Gorman, Chan, & Shum, 2016; Lawrence et al., 2004; Pineda, Ardila, & Rosselli, 1999; Seidman et al., 1997; Shue & Douglas, 1992), as confirmed in two meta-analyses (Walshaw, Alloy, & Sabb, 2010; Willcutt et al., 2005). During task-switching studies, ADHD patients show increased switch cost reaction time or errors relative to controls (Cao et al., 2013; King et al., 2007; Mor et al., 2015; Rubia, Smith, & Taylor, 2007).

Shared performance deficits during Stop (Goos, Crosbie, Payne, & Schachar, 2009; Schachar et al., 2005), Go/No-Go (Slaats-Willemse et al., 2003) and Stroop tasks (Slaats-Willemse et al., 2003) have been reported in unaffected first-degree relatives of ADHD patients. Deficits in inhibitory control are also state-independent. That is, they remain unchanged during symptom remission (McAuley, Crosbie, Charach, & Schachar, 2014).

### 2.1.5. Inhibitory control in OCD

The primary symptoms of OCD are intrusive obsessive thoughts and largely ego-dystonic compulsive rituals, and patients with OCD typically have good insight into the maladaptive outcomes associated with performance of compulsive rituals. Impaired response inhibition has therefore been hypothesised to underlie failures at regulating obsessions and compulsions in OCD (Chamberlain et al., 2005; Fineberg et al., 2014; Robbins et al., 2012).

In the case of response inhibition, a number of studies in adults have reported increased SSRT in patients with OCD compared with controls (Bersani, Quartini, Ratti, Pagliuca, & Gallo, 2013; Boisseau et al., 2012; Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006; Chamberlain, Fineberg, Menzies, et al., 2007; de Wit et al., 2012; Kang et al., 2013; Lei, Zhu, et al., 2015; McLaughlin et al., 2016; Menzies et al., 2007; Morein-Zamir, Fineberg, Robbins, & Sahakian, 2010; Morein-Zamir et al., 2014; Penadés et al., 2007; Sohn et al., 2014; van Velzen et al., 2015). A meta-analysis of six Stop task studies reported a medium effect size for impaired stop-signal in adults with OCD (Lipszyc & Schachar, 2010). Patients show impaired Go/No-Go performance (Abramovitch et al., 2012; Bannon, Gonsalvez, Croft, & Boyce, 2002, 2006; Penadés et al., 2007), and performance deficits in this task have also been reported in a sub-clinical OCD sample (Abramovitch, Shaham, Levin, Bar-Hen, & Schweiger, 2015), although meta-analyses of Go/No-Go tasks in adults with OCD report only a small to medium effect size for performance deficits in OCD patients (Snyder, Kaiser, Warren, & Heller, 2015; Wright et al., 2014).

In the case of interference inhibition, studies of adults with OCD have reported impaired performance in the Stroop task as indicated by slower reaction times and increased errors (Abramovitch et al., 2012; Aydin, Koybasi, Sert, Mete, & Oyekcin, 2014; Bannon et al., 2002; Demeter et al., 2013; Hartston & Swerdlow, 1999; Kashyap, Kumar, Kandavel, & Reddy, 2013; Ozcan, Ozer, & Yagcioglu, 2016; Pasini, Paloscia, Alessandrelli, Porfirio, & Curatolo, 2007; Rajender et al., 2011; Snyder et al., 2015; Tükel et al., 2012; Zhang, Yang, & Yang, 2015). These findings were confirmed in recent meta-analyses of Stroop studies in adults with OCD which reported medium effect sizes for increased interference effect on reaction time and errors in patients (Shin, Lee, Kim, & Kwon, 2014; Snyder et al., 2015). A study utilising a Simon task in OCD adults similarly found slower reaction times and increased errors in patients relative to controls (Penadés et al., 2007), although null findings

have also been reported (Marsh et al., 2014; Page et al., 2009; Woolley et al., 2008). Poor performance has also been reported in flanker tasks (Modirrousta, Meek, Sareen, & Enns, 2015).

Cognitive switching has been reported to be a feature of OCD, with impairments in cognitive flexibility hypothesised to lead to a failure to disengage from obsessive thoughts and compulsive behaviours (Chamberlain et al., 2005). Adult patients with OCD have been shown to demonstrate impaired performance in both the WCST and ID/ED (Aydin et al., 2014; Bannon et al., 2006; Bersani et al., 2013; Chamberlain et al., 2006; Chamberlain, Fineberg, Menzies, et al., 2007; de Geus, Denys, Sitskoorn, & Westenberg, 2007; Demeter et al., 2013; Fenger et al., 2005; Gruner et al., 2012; Kim et al., 2015; Lucey et al., 1997; Martin, Huber, Rief, & Exner, 2008; Morein-Zamir et al., 2014; Trivedi et al., 2008; Tükel et al., 2012; Watkins et al., 2005; Zhang, Yang, et al., 2015), as confirmed in recent meta-analyses (Abramovitch, Abramowitz, & Mittelman, 2013; Snyder et al., 2015). During task-switching, adult OCD patients show increased errors on switch trials compared with controls (Gu et al., 2008; Han et al., 2011), although null findings have also been reported (Page et al., 2009; Woolley et al., 2008). In a study by Britton and colleagues (Britton et al., 2010), paediatric OCD patients performed a task in which they had to indicate the odd stimulus out in a trio of stimuli. In non-switch blocks the dimension (colour or shape) on which participants had to select their responses stayed the same, whereas in switch blocks the dimension changed between trials. Children and adolescents with OCD showed a greater increase in reaction time in the switch block relative to the non-switch block, indicative of a higher switch cost.

Impairments in inhibitory control are shared with first-degree relatives (Cavedini, Zorzi, Piccinni, Cavallini, & Bellodi, 2010; Chamberlain, Fineberg, Menzies, et al., 2007; de Wit et

al., 2012; Menzies et al., 2007; Ozcan et al., 2016; Rajender et al., 2011; Zhang, Yang, et al., 2015), and remain in remitted OCD patients (Bannon et al., 2006; McLaughlin et al., 2016).

Impairments are more consistently found in adult than in children with OCD, with a recent meta-analysis of inhibitory control and switching in OCD children reporting no significant differences relative to controls (Abramovitch, Abramowitz, et al., 2015). One possible explanation for this is that poor performance in adults but not children in the disorder may reflect altered developmental trajectories and a failure to keep pace with normative performance which typically improves with age (Abramovitch, Abramowitz, et al., 2015). In line with this, previous work in paediatric OCD has shown neural activation was found to be a more sensitive measure of between group differences, which is indicative of alterations in brain networks responsible for inhibitory control in paediatric OCD (Rubia, Cubillo, et al., 2010; Rubia, Cubillo, Woolley, Brammer, & Smith, 2011; Woolley et al., 2008).

### 2.2. Sustained attention

Sustained attention refers to the ability to voluntarily maintain attention over prolonged periods of time in order to detect infrequently occurring stimuli (Parasuraman, Warm, & See, 1998; Warm, 1984). It is typically measured in stimulus detection paradigms, in which non-cued target stimuli are presented infrequently and separated by long inter-trial intervals (simple stimulus detection paradigms) or prolonged periods of non-target stimuli (continuous performance task, CPT) (Beck, Bransome, Mirsky, Rosvold, & Sarason, 1956; Christakou, Murphy, et al., 2013; Drummond et al., 2005; Langner et al., 2012). In the commonly used CPT-AX, participants ignore all letters except for the target letters, which are either typically an “A” followed by an “X” and a “A” followed by an “O” (Rubia, Smith, & Taylor, 2007). In all of these paradigms, the primary performance measure is number of omission errors.

Variations on sustained attention tasks include the Conners CPT and the Sustained Attention to Response Task (SART), in which the majority of trials require behavioural responses and a minority of trials require the withholding of responses. In these "reverse" sustained attention tasks, commission errors to infrequent no-go trials are assumed to be indicative of momentary lapses in sustained attention (Conners & Staff, 2000; Manly, Robertson, Galloway, & Hawkins, 1999; Robertson, Manly, Andrade, Baddeley, & Yiend, 1997).

Optimal task performance in sustained attention tasks requires participants to utilise top-down facilitation of target input and to maintain a preparation to respond (Shallice, Stuss, Alexander, Picton, & Derkzen, 2008). Peak levels of attentional alertness and readiness to respond cannot be maintained for longer than a few seconds, and task-set representations must be continuously reactivated during long delays (Langner & Eickhoff, 2013; Shallice et al., 2008). Well-learned simple repetitive tasks such as sustained attention tasks are often performed in absence of effortful executive attention processes, as responding becomes directed by behavioural schemata evoked in a largely bottom-up automatic manner by target input stimuli (Manly et al., 1999; Robertson et al., 1997). When tasks can be performed without effortful supervisory attention, attention is often instead directed toward self-generated, task-unrelated thought, or mind-wandering (Smallwood & Schooler, 2006). In such circumstances, due to a focus on internally generated thoughts at the expense of goal-directed attention, task performance becomes sub-optimal (Manly et al., 1999; Robertson et al., 1997).

### 2.2.1. Sustained attention in ADHD

In ADHD, poor concentration is a symptom of the disorder (American Psychiatric Association, 2013) and associated in particular with poor educational and workplace performance (Todd et al., 2002). Deficits in sustained attention are one of the most consistent

neuropsychological findings in ADHD (Brandeis et al., 2002; Kerns, McInerney, & Wilde, 2001; Klein, Wendling, Huettner, Ruder, & Peper, 2006; Oades, 2000; Rubia, Smith, & Taylor, 2007; Strandburg et al., 1996; Sunohara et al., 1999; Teicher, Lowen, Polcari, Foley, & McGreenery, 2004; van Leeuwen et al., 1998), as confirmed in multiple meta-analyses (Huang-Pollock et al., 2012; Losier, McGrath, & Klein, 1996; Mowinckel, Pedersen, Eilertsen, & Biele, 2015; Willcutt et al., 2005). The meta-analysis by Losier et al (Losier et al., 1996) of 26 studies using CPT reported significantly increased omission errors with a medium effect size in ADHD children and adolescents, which furthermore were partially ameliorated by methylphenidate medication. A subsequent meta-analysis of 30 CPT studies in ADHD children and adolescents reported similar performance deficits (Willcutt et al., 2005). The meta-analysis by Huang-Pollock et al (2012) of the 47 CPT studies in ADHD children and adolescents published subsequent to Losier et al literature search showed large effect sizes for differences in omission errors, commissions errors, reaction time and reaction time variability in ADHD relative to controls. A recent meta-analysis of 47 CPT studies reports a medium effect size for increased errors in ADHD adults relative to controls (Mowinckel et al., 2015).

In addition to studies using the CPT, studies using SART, Conner's CPT and simple stimulus detection paradigms have reported increased reaction times, reaction time variability and commission errors in paediatric ADHD (Christakou, Murphy, et al., 2013; Epstein et al., 2003; Johnson et al., 2007). Performance deficits during CPT have also been unreported in unaffected first degree relatives of ADHD patients (Pironti et al., 2014). There also exists indirect evidence for sustained attention deficits in ADHD. For instance, ADHD is associated with increased reports of mind-wandering both during experience sampling while completing a CPT (Shaw & Giambra, 1993) and as a trait-like individual difference on self-report measures (Mowlem et al., 2016; Seli, Smallwood, Cheyne, & Smilek, 2015), and patients

with ADHD self-report impairments in executive attention (Malloy-Diniz, Fuentes, Leite, Correa, & Bechara, 2007; Nandagopal et al., 2011).

### 2.2.2. Sustained attention in OCD

In OCD, a difficulty in sustaining attention towards external goal-relevant stimuli is a plausible neurocognitive mechanism that may underlie difficulties in disengaging from internally generated obsessional thoughts (Clayton et al., 1999; Seli et al., 2016). In line with this, studies report impaired performance on sustained attention tasks in OCD (Baykal et al., 2014; Bersani et al., 2013; Morein-Zamir, Craig, et al., 2010; Rajender et al., 2011; Trivedi et al., 2008), although a minority of studies report negative findings (Milliery, Bouvard, Aupetit, & Cottraux, 2000), and two recent meta-analyses reported a medium effect size for increased omission errors in six studies comparing OCD adults and controls during sustained attention (Abramovitch et al., 2013; Shin, Lee, et al., 2014). Deficits in sustained attention have been reported in OCD youth (Baykal et al., 2014), although negative results also exist in the literature (Shin et al., 2008). Similar to patients with ADHD, patients with OCD self-report elevated levels of mind-wandering (Seli et al., 2016), as well as impairments in executive attention (Armstrong, Zald, & Olatunji, 2011; Benatti, Dell'Osso, Arici, Hollander, & Altamura, 2014; Grassi et al., 2015; Sohn et al., 2014).

## 2.3. Reward-related decision-making

Decision-making tasks most commonly studies in ADHD and OCD can largely be divided into three categories. Temporal decision-making tasks measure the effects of delay on the subjective value of rewards, and involve deciding between a small immediate or soon to be awarded reward and a large delayed one (McClure, Laibson, Loewenstein, & Cohen, 2004; Noreika et al., 2013; Scheres, de Water, & Mies, 2013). Choice impulsivity refers to an

exaggerated preference for sooner smaller rewards (Hamilton et al., 2015). Risky decision-making tasks involve an explicit choice between a small but highly probable reward and a larger reward that is less probable (Brand et al., 2005; Dekkers, Popma, Agelink van Rentergem, Bexkens, & Huizenga, 2016; Groen et al., 2013; Rogers et al., 1999). In tasks measuring decision-making under ambiguity, participants choose under conditions where the exact choice-outcome contingencies are not provided explicitly, and instead must be learned over the course of the task (Bechara, Damasio, Damasio, & Anderson, 1994; Bechara, Damasio, Damasio, & Lee, 1999; Bechara, Damasio, Tranel, & Damasio, 1997; Christakou, Brammer, Giampietro, & Rubia, 2009; Dekkers et al., 2016; Groen et al., 2013).

The most commonly used task of temporal decision-making is the experiential delay discounting task, in which participants experience real delays which can be short (e.g., 2 seconds) or long (e.g., up to 60 seconds) and associated with real rewards (e.g., points or monetary rewards). When participants choose the longer delay, they receive larger rewards than when they choose the short delay (Sonuga-Barke, Taylor, Sembi, & Smith, 1992). In the more recently developed temporal discounting (TD) tasks (Christakou, Brammer, & Rubia, 2011; Hamilton et al., 2015; Peters & Buchel, 2011), participants are provided with a series of typically hypothetical choices between small immediate rewards and larger rewards available after a temporal delay, typically ranging from weeks to years. TD refers to the fact that the subjective values of rewards available after a temporal delay decrease as a function of the length of the temporal delay (Christakou et al., 2011; Hamilton et al., 2015). In studies incorporating adjusting-amount procedures (Carlisi et al., 2016; Christakou et al., 2011; Richards, Mitchell, de Wit, & Seiden, 1997), adjustments of the immediate reward magnitude are performed according to the individual participant's previous choices using an online algorithm, such that the range of options are narrowed around the point where the subjective value of the immediate reward is equal to that of fixed delayed reward (the indifference

point) (Carlisi et al., 2016; Christakou et al., 2011; Richards et al., 1997). Indifference points across different delay lengths are used to produce a discounting curve, which is typically hyperbolic (i.e., as delay periods become longer, the rate at which reward values are declined decreases more drastically) (Peters & Buchel, 2011). The subjective value of reward on the TD task can be described using a hyperbolic decay function, and estimated using the equation $V = A/(1 + kD)$, where V is the subjective value of a reward, A is size of the reward, D is the delay until reward receipt, and *k* is a constant which characterizes an individual's rate of discounting, and which is calculated by fitting a hyperbolic function to the indifference values for every delay (Christakou et al., 2011; Richards, Zhang, Mitchell, & de Wit, 1999). Larger *k* values indicate steeper discounting (Richards et al., 1999) and steepness of discounting curves varies widely between individuals (Hamilton et al., 2015; Peters & Buchel, 2011).

The most commonly used tasks for measuring risky decision-making are the Cambridge Gambling Task (CGT) and Game of Dice Task (GDT) (Brand et al., 2005; Rogers et al., 1999). On each trial of the CGT, participants are provided with 10 boxes some of which are red and some of which are blue, with the ratio of red to blue boxes changing across trials (6:4, 7:3, 8:2, 9:1). Inside one of the coloured boxes is a token, and participants choose which colour to bet on and how much to wager (5%, 25%, 50%, 75% or 95% of current points). The main outcomes are the rate at which subjects increase the bet proportion in response to more favourable ratios (risk adjustment) and the average number of points wagered (risk proneness) (Rogers et al., 1999). In the GDT, participants have to guess which number will appear on a rolled dice. They can choose between a single number and a combination of two, three or four numbers. Each choice is associated with different magnitudes of gains and losses ($1000 for single number, $500 for two numbers, $200 gain/loss for three numbers and $100 for four numbers). Choosing one or two numbers has less than a 50% chance of

winning, and is therefore considered risky decision-making. Choosing three or more numbers provides a 50% or greater chance of winning, and therefore such choices are considered safe. The primary outcome is the proportion of safe to risky choices (Brand et al., 2005).

The primary task for measuring decision-making under ambiguity is the Iowa Gambling Task (IGT), in which participants are presented with four decks of playing cards, and instructed to select cards, one at a time, from any of the decks (Bechara et al., 1994; Bechara et al., 1999; Bechara et al., 1997). Each card is associated with a 50% chance of a monetary win or loss. Disadvantageous decks provide big wins but even bigger losses, whereas advantageous decks provide smaller wins but even smaller losses. Participants are not instructed as to the nature of the decks, and must establish over successive choices that choosing cards from the advantageous decks provides an overall net benefit. The primary outcome is the proportion of advantageous versus disadvantageous decisions (Bechara et al., 1994; Bechara et al., 1999; Bechara et al., 1997).

### 2.3.1. Reward-related decision-making in ADHD

A large number of studies have reported more impulsive decision-making in ADHD in both experiential delay (Bitsakou, Psychogiou, Thompson, & Sonuga-Barke, 2009; Coghill, Seth, & Matthews, 2014; Metin et al., 2016; Patros et al., 2016; Patros, Alderson, Lea, & Tarle, 2015; Scheres, Tontsch, Thoeny, & Kaczkurkin, 2010; Solanto et al., 2001; Sonuga-Barke et al., 1992; Vloet, Marx, et al., 2010; Yang et al., 2011) and TD tasks (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Carlisi et al., 2016; Castellanos-Ryan et al., 2014; Demurie, Roeyers, Baeyens, & Sonuga-Barke, 2012; Fassbender et al., 2014; Hoogman et al., 2011; Hurst, Kepley, McCalla, & Livermore, 2011; Jackson & MacKillop, 2016; Mostert et al., 2015; Paloyelis, Asherson, Mehta, Faraone, & Kuntsi, 2010; Patros et al., 2016; Wilson, Mitchell, Musser, Schmitt, & Nigg, 2011). A meta-analysis of 28 studies using experiential

delay and TD tasks comparing patients with ADHD and controls reported reliably increased choice impulsivity in ADHD with a medium effect size (Patros et al., 2016). A subsequent meta-analysis of 25 case-control comparisons during TD tasks reported significantly steeper discounting with a medium effect size (Jackson & MacKillop, 2016). Choice impulsivity has therefore been considered one of the primary neuropsychological deficits in ADHD, and hypothesised to result from failures of future reinforcement signalling to delayed rewards, increased negative emotions associated with waiting for reward (delay aversion), and impairments in regulatory control or temporal foresight in ADHD (Noreika et al., 2013; Rubia, Halari, Christakou, & Taylor, 2009; Sonuga-Barke, Cortese, Fairchild, & Stringaris, 2016).

ADHD is associated with increased risk taking, including risky driving behaviours (Jerome, Segal, & Habinski, 2006), risky sexual behaviours (Sarver, McCart, Sheidow, & Letourneau, 2014), and substance-abuse (Young & Sedgwick, 2015), which may plausibly result from increased thrill seeking and impaired self-control (Jerome et al., 2006; Sorensen et al., 2016; Young & Sedgwick, 2015). In line with this, a number of studies using explicit risk taking tasks have found evidence for increased risky decision-making in ADHD. Two studies reported poorer risk adjustment in adolescent ADHD patients using the CGT (DeVito et al., 2008; Sorensen et al., 2016), while another study found that the risk adjustment score loaded on a decision-making factor, which was impaired in patients with ADHD (Coghill et al., 2014). Similarly, in the GDT patients with ADHD have been found to make a greater number of risky choices (Matthies, Philipsen, & Svaldi, 2012), although negative findings are also available in the literature for both tasks (Kroyzer, Gross-Tsur, & Pollak, 2014; Pollak & Shoham, 2015; Wilbertz et al., 2012). However, recent literature questions whether risk seeking is a feature of ADHD. First, patients with ADHD are not more risk prone. That is, they do not tend to make larger bets than controls (DeVito et al., 2008; Sorensen et al., 2016),

and there is some evidence that they may actually choose smaller wagers during CGT (Kroyzer et al., 2014; Pollak & Shoham, 2015). Second, performance differences are found only in a version of the CGT with feedback (DeVito et al., 2008; Sorensen et al., 2016), but not in a version of the task without feedback (Pollak & Shoham, 2015). Third, in the typical version of the CGT, wager options are presented consecutively in either ascending or descending order. ADHD patients make more delay averse choices. That is, they tend to choose the wager options presented early in the series rather than wait for later options, with this preference correlating with risk adjustment scores (Sorensen et al., 2016), and ADHD patients do not show abnormal risk adjustment in a version of the task which presents wager options simultaneously (Kroyzer et al., 2014). Fourth, in a series of studies examining responses to decisions involving certain and risky alternatives matched for expected values, it was found that patients with ADHD did not choose the risky alternatives more often than controls (Pollak et al., 2016). Finally, a recent meta-analysis of explicit risk taking in ADHD failed to report a significant difference in performance between patients and controls (Dekkers et al., 2016). Findings therefore suggest that ADHD may be more characterized by abnormal feedback processing, reduced deliberation times, and increased delay aversion rather than risk seeking *per se.*

Patients with ADHD may also be characterized by a failure to adequately learn behavior-outcome contingencies and to use these to guide behavior (Tripp & Wickens, 2008; Tripp & Wickens, 2009). Supporting this, a number of ambiguous decision-making using IGT and related tasks report impaired performance in ADHD (Abouzari, Oberg, & Tata, 2016; Agay, Yechiam, Carmel, & Levkovitz, 2010; Baker, 2011; Dekkers et al., 2016; Ernst, Grant, et al., 2003; Garon, Moore, & Waschbusch, 2006; Hobson et al., 2011; Malloy-Diniz et al., 2007; Malloy-Diniz et al., 2008; Mantyla, Still, Gullberg, & Del Missier, 2012; Medrano et al.,

2015; Miller, Sheridan, Cardoos, & Hinshaw, 2013; Toplak, Jain, & Tannock, 2005), as confirmed in a recent meta-analysis (Dekkers et al., 2016).

### 2.3.2. Reward-related decision-making in OCD

To date, only three studies have examined TD in OCD (Pinto et al., 2016; Sohn et al., 2014; Vloet, Marx, et al., 2010). First, a study using an experiential delay procedure failed to find a difference between adolescent OCD patients and healthy controls (Vloet, Marx, et al., 2010). Pinto et al. used a single delay (i.e., 3 months) and discount factor (δ) as a discount parameter, finding no significant difference between OCD patients and controls. However the only study to use an adjusting-amount procedure with multiple levels of delay in OCD patients found significantly steeper discounting ($k$) in adult OCD patients relative to controls (Sohn et al., 2014). Increased choice impulsivity is predicted in recent models of OCD that propose that behaviours associated with compulsive symptoms, which patients with OCD predict will relieve anxiety and increase positive emotions (Fontenelle et al., 2015), are performed to bring about an initially rewarding outcome despite the negative long-term consequences (Cavedini et al., 2002; Grassi et al., 2015; Sohn et al., 2014).

There is limited evidence for performance deficits in explicit risk-taking tasks in OCD. For instance, multiple studies report unimpaired performance on the CGT and GDT (Anger et al., 2016; Chamberlain, Fineberg, Blackwell, et al., 2007; Chamberlain, Fineberg, Menzies, et al., 2007; Kim et al., 2015; Morein-Zamir et al., 2014; Starcke, Tuschen-Caffier, Markowitsch, & Brand, 2009, 2010; Watkins et al., 2005; Zhang, Dong, Ji, Tao, et al., 2015; Zhang, Dong, Ji, Zhu, et al., 2015), although see Dittrich & Johansen (2013) for an exception.

A large number of studies have examined IGT performance, with the majority finding significant performance impairments in OCD patients relative to controls (Cavedini et al., 2002; Cavedini et al., 2012; da Rocha, Alvarenga, Malloy-Diniz, & Correa, 2011; Grassi et

al., 2015; Kashyap et al., 2013; Kim et al., 2015; Kodaira et al., 2012; Martoni et al., 2015; Starcke et al., 2009, 2010; Zhang, Dong, Ji, Tao, et al., 2015; Zhang, Dong, Ji, Zhu, et al., 2015), including in adolescents (Kodaira et al., 2012). Impaired performance has also been reported in healthy first-degree relatives of OCD patients (Cavedini et al., 2010; Viswanath, Janardhan Reddy, Kumar, Kandavel, & Chandrashekar, 2009; Zhang, Dong, Ji, Zhu, et al., 2015). Indeed some studies have reported impaired ambiguous decision-making but unaffected explicit risk taking in the same samples of OCD patients and healthy first-degree relatives (Kim et al., 2015; Starcke et al., 2009, 2010; Zhang, Dong, Ji, Tao, et al., 2015; Zhang, Dong, Ji, Zhu, et al., 2015). Such a dissociation suggests that poor performance on the IGT in OCD likely results from failures in orbito-striato-limbic dependent emotional learning of behaviour-outcome contingencies, which has been found to be impaired in OCD, rather than increased risk-seeking (Kim et al., 2015; Remijnse, Nielen, Balkom, et al., 2006; Remijnse et al., 2009; Starcke et al., 2010). Interestingly, poor IGT performance has been found to predict poor treatment outcome following SSRI treatment, perhaps suggesting that the IGT taps into key mechanisms which are important for OCD symptom maintenance (Cavedini et al., 2002).

### 2.4 Additional cool EF findings in ADHD

Patients with ADHD show working memory impairments as indicated by significantly lower scores and greater number of errors during digit and spatial span tasks on both the forward and backwards components (Alderson, Kasper, Hudec, & Patros, 2013; Martinussen & Tannock, 2006; Pasini et al., 2007; Rapport et al., 2008; Stevens, Quittner, Zuckerman, & Moore, 2002), as well as a significantly increased omission errors and intra-subject variability with increasing working memory load during N-Back tasks (Alderson et al., 2013; Klein et al., 2006; Pasini et al., 2007).

A number of studies have further reported deficits in planning in ADHD patients, as assessed using Tower of London tasks and related tasks (Gau, Chiu, Shang, Cheng, & Soong, 2009; Toplak, Bucciarelli, Jain, & Tannock, 2009).

### 2.5. Additional cool EF findings in OCD

Working memory performance is also impaired in OCD, as assessed using digit and spatial span and N-Back tasks (Abramovitch et al., 2013; Shin, Lee, et al., 2014; Snyder et al., 2015).

Studies examining planning tasks such as the Tower of London task also report reliable performance deficits in OCD (Abramovitch et al., 2013; Shin, Lee, et al., 2014; Snyder et al., 2015).

Patients with OCD have also shown performance deficits in the Trail Making Task Part A, suggestive of deficits in focused attention (Abramovitch et al., 2013; Kashyap et al., 2013; Rajender et al., 2011; Roh et al., 2005; Shin, Lee, et al., 2014; Snyder et al., 2015; Tükel et al., 2012).

### 2.6. Additional hot EF findings in ADHD

Patients with ADHD appear to benefit more than healthy controls from the motivating benefits of rewards during cognitive tasks (Luman, Oosterlaan, & Sergeant, 2005). However, this benefit may be restricted to situations where reward feedback is entirely explicit and informative, as patients with ADHD have demonstrated impaired performance on tasks involving probabilistic reward schedules (Groen et al., 2008; Luman et al., 2009; Tripp & Alsop, 1999).

## 2.7. Additional hot EF findings in OCD

There is evidence that patients with OCD show deficits in ventromedial orbitofrontal cortex (vmOFC) dependent "hot EF" processes, including reward-reversal learning and fear extinction retrieval (Aycicegi, Dinn, Harris, & Erkmen, 2003; Endrass, Koehne, Riesel, & Kathmann, 2013; Kim et al., 2015; Milad et al., 2013; Remijnse, Nielen, Balkom, et al., 2006). Both of these tasks require integration of vmOFC with striato-limbic regions in order to respond according to updated stimulus-outcome contingencies, supporting that such processes are impaired in OCD (Kim et al., 2015).

Patients with OCD also show enhanced habitual responding at the expense of goal-directed responding (Gillan et al., 2015; Gillan et al., 2014; Gillan et al., 2011; Gillan & Robbins, 2014). This was first showed in an appetitive instrumental learning task where, following devaluation (by instructing participants that particular outcomes no longer provided points), patients with OCD had difficulty refraining from making responses that now yielded devalued outcomes. Participants also self-reported impaired explicit awareness of stimulus-outcome contingencies (Gillan et al., 2011). Similarly, using an instrumental fear avoidance paradigm, in which participants learn to avoid shocks by making a correct response to warning stimuli, it has been shown that, following devaluation of one of the warning stimuli (removing the associated stimulator from one of the participants wrists), patients with OCD are more likely to continue to make avoidance responses to the devalued stimulus (Gillan et al., 2015; Gillan et al., 2014). Studies using a two-step sequential learning task have also shown that, in the context of reward learning, patients with OCD make fewer model-based responses dependent on higher-order knowledge of task structure and behaviour-outcome contingencies, and instead respond more often according to recent reinforcement history

(Voon, Baek, et al., 2015; Voon, Derbyshire, et al., 2015), although the opposite finding is true when learning to avoid punishments (Voon, Baek, et al., 2015).

### 2.8. Summary of executive function in ADHD and OCD

The most commonly studied executive function in ADHD and OCD is inhibitory control. Both disorders show performance deficits across response inhibition, interference inhibition and switching, which are proposed to underlie deficits in controlling impulsive behaviours in ADHD and obsessions and compulsions in OCD (Abramovitch et al., 2013; Alderson et al., 2007; Homack & Riccio, 2004; Lansbergen et al., 2007; Lijffijt et al., 2005; Lipszyc & Schachar, 2010; Mullane et al., 2009; Oosterlaan et al., 1998; Shin, Lee, et al., 2014; Snyder et al., 2015; Walshaw et al., 2010; Willcutt et al., 2005; Wright et al., 2014).

Sustained attention has been extensively studied in ADHD, and found to be reliably impaired in both adolescents and adults with the disorder (Huang-Pollock et al., 2012; Losier et al., 1996; Mowinckel et al., 2015; Willcutt et al., 2005). There are fewer studies in OCD, and the most have focused on adults with the disorder. However, the majority of studies in adults and a study in adolescents have reported performance deficits in OCD patients during sustained attention (Abramovitch et al., 2013; Shin, Lee, et al., 2014).

Regarding reward-related decision-making, impulsive decision-making has been reliably reported in ADHD, in both experiential delay and TD tasks and in both adults and adolescents with the disorder (Huang-Pollock et al., 2012; Patros et al., 2016). In OCD, only one study has examined has examined TD using an adjusting-amount procedure with multiple levels of delay, reporting relatively impulsive decision-making in OCD adults (Sohn et al., 2014). Patients with ADHD and OCD do not appear to demonstrate increased risky decision-making in explicit risk taking tasks (Dekkers et al., 2016; Kim et al., 2015; Starcke et al., 2009; Zhang, Yang, et al., 2015). However, both disorders demonstrate performance deficits

in the IGT that measures decision-making under ambiguity (Dekkers et al., 2016; Kim et al., 2015; Starcke et al., 2009; Zhang, Yang, et al., 2015).

Deficits in these executive function domains are also found in unaffected first-degree relatives of ADHD and OCD patients and in remitted patients post-treatment, suggesting that performance deficits are not simply an epiphenomenal consequence of ADHD and OCD symptoms, and potentially may be endophenotypes associated with increased genetic risk for the two disorders (Goos et al., 2009; McAuley et al., 2014; Robbins et al., 2012).

In ADHD, these domains are well studied in adolescents and adults with the disorder. However, in OCD, the majority have focused on adult patients, with only a small number of published studies examining deficits in younger age groups.

**Chapter 3. Abnormalities in brain structure and function in ADHD and OCD.**

Neuroimaging refers to the process of measuring brain structure, function and neurochemistry.

Brain structure is typically measured using structural magnetic resonance imaging (sMRI), and is typically used to assess group differences or development of grey and white matter, using either region of interest (ROI), or more recently, whole brain voxel-wise methods. The brain goes through a protracted maturation, which lasts through adolescence and into early adulthood (Rubia, 2013). Longitudinal scans of typically developing children and adolescents demonstrate increasing white matter volume (WMV) volumes but inverted U-shaped trajectories of grey matter volume (GMV), which peaks during adolescence and then declines through late adolescence and adulthood, with peak sizes occurring in different regions.at different times (Blakemore, 2012; Giedd & Rapoport, 2010; Paus et al., 2001). There is a linear relationship between GMV and WMV development and EF (Blakemore, 2012; Kharitonova, Martin, Gabrieli, & Sheridan, 2013). Moreover, differences in GMV and WMV exist between individuals, have been detected between patient groups and controls, and found to correlate with performance on EF measures, including in ADHD and OCD patients (Casey et al., 1997; Depue, Burgess, Bidwell, Willcutt, & Banich, 2010 Willcutt, & Banich, 2010; Menzies et al., 2007; Pironti et al., 2014). Understanding structural brain abnormalities in ADHD and OCD may therefore aid understanding of the neuroanatomical basis of impaired EF in each disorder.

Functional neuroimaging is used to observe the brain activation either during resting-state or during a task. A majority of functional neuroimaging studies in the ADHD and OCD literature have used functional magnetic resonance imaging (fMRI) to study group differences in brain activation between patients and control groups. This is because fMRI has numerous advantages over alternative functional neuroimaging methods. It has a much better

spatial resolution relative to electroencephalography (EEG), event-related potentials (ERPs) and functional near-infrared spectroscopy (fNIRS), and unlike these methods allows for the study of subcortical structures including the basal ganglia, which are implicated heavily in ADHD and OCD (Menzies et al., 2008; Poldrack, Mumford, & Nichols, 2011; Rubia, Alegria, & Brinson, 2014). Functional MRI also has a relatively superior temporal resolution relative to Positron-Emission Tomography (PET), and unlike PET is non-invasive as it does not require injection of isotopes, thus making this method safe and ethical for use in children (Poldrack et al., 2011).

There is a large literature base of existing studies that have attempted to elucidate the neuroanatomical basis of each disorder by using neuroimaging methods to compare ADHD or OCD patients against controls on brain structure and function. Given the aims of this PhD, research in ADHD and OCD using sMRI to examine GMV abnormalities and fMRI studies of inhibitory control, sustained attention and reward-related decision-making are focused upon in the current review.

### 3.1. Structural abnormalities in ADHD

Both paediatric and adult patients with ADHD show total cerebral volume, total white and total grey matter volume decreases of around 3-8% relative to healthy controls (Batty et al., 2010; Biederman et al., 2008; Brieber et al., 2007; Carmona et al., 2005; Castellanos et al., 1996; Castellanos et al., 2002; Greven et al., 2015; Lim et al., 2015; Maier et al.; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002; Silk et al., 2016; Valera, Faraone, Murray, & Seidman, 2007). A large study of 307 paediatric and adult patients with ADHD, 169 of their unaffected siblings, and 196 typically healthy controls showed that patients with ADHD had reductions in total brain volume, total WMV and total GMV of around 3% relative to

controls. The unaffected siblings showed total brain and total GMV that were intermediate to participants with ADHD and control individuals (Greven et al., 2015). Reduced overall cortical thickness, cortical surface and cortical folding have also been reported (Shaw et al., 2006; Silk et al., 2016; Wolosin, Richardson, Hennessey, Denckla, & Mostofsky, 2009).

Reduced basal ganglia GMV is a common finding in ADHD (Anqi Qiu et al., 2009; Castellanos et al., 1996; Filipek et al., 1997; Lim et al., 2013; Montes et al., 2011; Onnink et al., 2014; Proal et al., 2011; Roman-Urrestarazu et al., 2016; Sobel et al., 2010; van Wingen et al., 2013). Meta-analyses of ROI and whole-brain voxel-based morphometry (VBM) studies of region grey matter volume have reported reliable reductions in basal ganglia GMV in patients with ADHD (Ellison-Wright, Ellison-Wright, & Bullmore, 2008; Frodl & Skokauskas, 2012; Nakao, Radua, Rubia, & Mataix-Cols, 2011; Valera et al., 2007). In the most recent meta-analysis of VBM studies in ADHD by Frodl and Skokauskas, reduced GMV in right putamen and globus pallidus was reproduced in children with ADHD, but significant GMV reduction in these regions was not found in adults. However, this may be due to the small number of adult studies (four), and subsequent work has reported reduced GMV in ADHD adult patients (Montes et al., 2011; Onnink et al., 2014; Proal et al., 2011; Roman-Urrestarazu et al., 2016; Seidman et al., 2011; van Wingen et al., 2013). In a comparison of twins discordant for ADHD, affected twins had significantly smaller caudate volume than unaffected twins, suggesting reduced caudate volume is associated with disease state or non-shared environmental risk for ADHD (Castellanos et al., 2003).

The basal ganglia are important components of fronto-striatal circuits which mediate cognitive functions such as inhibitory control and sustained attention. This suggests that GMV abnormalities in these regions may be underlie performance impairments in these EF domains in ADHD patients. In line with this, reductions in basal ganglia volume have been

found to correlate with impaired inhibitory control in ADHD children (Casey et al., 1997; McAlonan et al., 2009).

In frontal lobe, patients with ADHD show decreased overall total GMV and WMV relative to age matched controls (Biederman et al., 2008; Mostofsky et al., 2002), and reductions in frontal lobe white and grey matter in the frontal lobe has been reported to account for 48% of the total decrease in cerebral volume in ADHD patients (Mostofsky et al., 2002). Reduced GMV has been reported throughout prefrontal cortex in both children and adults with ADHD (Durston et al., 2004; Greven et al., 2015; Lim et al., 2013; Pironti et al., 2014). Poor performance in inhibitory control and sustained attention tasks has been shown to be associated with reduced inferior frontal gyrus (IFG) volume in both paediatric and adult patients with ADHD (Casey et al., 1997; Depue et al., 2010; Pironti et al., 2014).

Although not traditionally hypothesised in theoretical accounts of ADHD, a number of studies have found decreased GMV in vmOFC (Bralten et al., 2016; He et al., 2015; Hesslinger et al., 2002; Kappel et al., 2015; Maier et al.). An association between vmOFC volume and ADHD symptoms has also been reported in a comparison of healthy twin pairs concordant for heightened ADHD symptoms with twin pairs concordant for low symptoms (van ’t Ent et al., 2007). In a recent large study of 307 adolescent and adult patients with ADHD, 169 unaffected siblings and 196 healthy controls, the only decrease in prefrontal GMV in patients was in vmOFC. Unaffected siblings also showed significantly decreased vmOFC volumes that were intermediate between those reported in patients with ADHD and healthy controls, and across the entire sample vmOFC volume decreased with increasing ADHD symptoms (Bralten et al., 2016). In non-ADHD samples, smaller vmOFC has been associated with poorer performance on fear extinction (Hartley, Fischl, & Phelps, 2011; Milad et al., 2005), emotion interference (Deng et al., 2014), cognitive reappraisal (Welborn et al., 2009), and reward-related decision-making tasks (Le Berre et al., 2014; Tanabe et al.,

2013). Decreased vmOFC volume in ADHD may therefore underlie deficits in regulating affect, motivation, and impulsive decision-making (Bralten et al., 2016; He et al., 2015).

Work by Shaw and colleagues utilising a cohort of 231 control children and 234 children with ADHD scanned up to four times between the during childhood and adolescence points to a developmental delay in cortical thickness and surface area particularly within late developing lateral prefrontal cortex in ADHD (Shaw et al., 2011; Shaw et al., 2006; Shaw et al., 2013; Shaw et al., 2012). In the case of cortical thickness, both the patient group and controls showed similar developmental trajectories, showing that cortical thickness and surface area increased between childhood and adolescence due to synaptic and axonal branching, with healthy children reaching peak thickness and surface area at age 7 and 13 years respectively. Following this, decreases were seen in cortical thickness and surface area, presumably reflecting synaptic pruning and myelination (Shaw et al., 2011; Shaw et al., 2006; Shaw et al., 2013; Shaw et al., 2012). For both cortical thickness and surface area, primary sensory areas mature earlier than polymodal, high-order association areas. ADHD patients showed similar patterns of development, although maturation was delayed by around two years on average in most cortical regions and up to five years in lateral prefrontal cortex and up to 4 years in temporal brain regions (Shaw et al., 2013; Shaw et al., 2012). Similar delays were found to correlate with ADHD symptoms in healthy participants, supporting a dimensional model of ADHD (Shaw et al., 2011). Decreased vmOFC cortical thickness in childhood was found to predict poorer outcomes in adolescence (Shaw et al., 2006).

Decreased volume of the cerebellum is also a consistent finding in ROI studies of GMV in ADHD (Biederman et al., 2008), as confirmed in the meta-analysis by Valera and colleagues (2007), and has been reported in a number of whole-brain VBM studies (Bonath, Tegelbeckers, Wilke, Flechtner, & Krauel, 2016; Lim et al., 2015; Lim et al., 2013; Proal et al., 2011). Although traditionally implicated in motor-control, fMRI studies have

demonstrated a role for the cerebellum in executive functions including inhibitory control, sustained attention and decision-making (Christakou, Murphy, et al., 2013; Rubia, Halari, Christakou, et al., 2009; Rubia et al., 2013; Rubia, Smith, Taylor, & Brammer, 2007; Stoodley & Schmahmann, 2009), as well as timing functions (Noreika et al., 2013; Rubia, Halari, Christakou, et al., 2009). Cerebellar deficits are specific to ADHD patients relative to unaffected siblings (Durston et al., 2004). Similarly, in a study of twins discordant on ADHD symptoms, twins who scored highly for ADHD symptoms had significantly smaller cerebellum compared with twins without significant ADHD symptoms (van 't Ent et al., 2007). Together, these findings suggest that reduced cerebellum is associated with disease state or non-shared environmental risk rather than representing a possible endophenotype for ADHD (Durston et al., 2004; van 't Ent et al., 2007). In a longitudinal case-control study of 36 children with ADHD and 36 healthy controls, poorer outcome was associated with smaller cerebellar volume at baseline and an altered developmental trajectory, wherein patients with poorer outcomes showed progressively smaller cerebellar volumes relative to patients with better outcomes and healthy controls (Mackie et al., 2007).

### 3.2. Structural abnormalities in OCD

There is no consistent evidence for global abnormalities in brain total cerebral volume, total WMV and total GMV (de Wit et al., 2014; Fouche et al., 2016; Radua & Mataix-Cols, 2009; Radua et al., 2010).

In OCD, the most consistent subcortical abnormality is increased GMV in basal ganglia. This has been reported in both paediatric (Gilbert, Keshavan, et al., 2008; Szeszko et al., 2008; Zarei et al., 2011) and adult OCD patients (Hou et al., 2013; Menzies et al., 2007; Narayanaswamy, Jose, Kalmady, Venkatasubramanian, & Janardhana Reddy, 2013; Pujol et al., 2004; Real et al., 2016; Subira et al., 2013; Tang et al., 2013; Yoo et al., 2008) and

confirmed in meta-analyses of VBM studies (Peng et al., 2012; Radua & Mataix-Cols, 2009; Radua et al., 2010). Most studies implicate enlarged putamen, although enlarged caudate volumes have also been reported in OCD (Hou et al., 2013; Narayanaswamy et al., 2013; Zarei et al., 2011). In paediatric patients, increased putamen correlates with symptom severity (Szeszko et al., 2008; Zarei et al., 2011). A large multi-centre mega-analysis of 412 adult OCD patients and 368 healthy controls reported a significant age by group interaction in the right putamen and nucleus accumbens, which in controls showed decreasing GMV with increasing age whereas in OCD patients GMV was preserved with increasing age (de Wit et al., 2014). Enlarged putamen volumes correlate with OCD symptoms in healthy participants (Kubota et al., 2016), and has also been found to be shared with in adult unaffected first degree relatives (Menzies et al., 2007), although this was not replicated in child and adolescent relatives (Gilbert, Keshavan, et al., 2008).

Within prefrontal cortex, decreased GMV has been reported in rostral/dorsal medial prefrontal cortex including anterior cingulate cortex (r/d MPFC/ACC), in paediatric (Carmona et al., 2007; Chen, Silk, Seal, Dally, & Vance, 2013; Gilbert, Keshavan, et al., 2008; Jayarajan et al., 2015) and adult patients with OCD (de Wit et al., 2014; Gilbert, Mataix-Cols, et al., 2008; Koprivova et al., 2009; Menzies et al., 2007; Pujol et al., 2004; Togao et al., 2010; Valente et al., 2005; van den Heuvel et al., 2009; Yoo et al., 2008), as confirmed in meta-analyses of ROI and whole-brain studies of GMV (Peng et al., 2012; Radua & Mataix-Cols, 2009; Radua et al., 2010; Rotge et al., 2009) and in the aforementioned mega-analysis by De Wit and colleagues (2014).

In paediatric studies, enlarged orbitofrontal cortex (OFC) volume has been reported in both lateral (Szeszko et al., 2008) and medial subdivisions (Britton et al., 2010; Christian et al., 2008; Huyser et al., 2014) and in a large study of 1639 healthy adolescents increased OFC volume correlates was found to correlate with a compulsivity composite measure based on

OCD and eating disorder symptoms (Montigny et al., 2013). In adults with OCD, in both lOFC and vmOFC increased and decreased volume has been reported. Reasons for heterogeneity in OFC abnormalities are unclear, although OFC volume has been found to be associated with symptom duration (Brooks et al., 2015), exposure to childhood trauma (Brooks et al., 2015), comorbid depression (Christian et al., 2008) and treatment with CBT (Atmaca et al., 2016; Huyser et al., 2013). A longitudinal study by Huyser and colleagues (2014) reported that in healthy adolescents, OFC GMV decreased during the study's two year time period, but increased in adolescent patients with OCD over the same time period. Alterations in OFC maturation was also suggested by the mega-analysis by De Wit and colleagues (2014), who found decreasing OFC GMV with increasing age in healthy adults, but in adults with OCD OFC was preserved over time.

A study by Menzies and colleagues (2007) reported that this pattern of decreased GMV in dorsal ACC, vmOFC, IFG and dorsolateral prefrontal cortex (DLPFC) and increased GMV in bilateral putamen and caudate in OCD correlated with impaired performance in a Stop task in a sample of adult OCD patients, unaffected first-degree relatives and healthy controls, suggesting that these structural GMV abnormalities lead to impairments in fronto-striatal mediated functions.

### 3.3. Functional neuroimaging of inhibitory control in ADHD

Within prefrontal cortex, the most consistently implicated area in ADHD is the IFG. Primarily right but also left IFG underactivation has been reported in Stop (Cubillo et al., 2014b; Hart, Chantiluke, et al., 2014; Janssen, Heslenfeld, van Mourik, Logan, & Oosterlaan, 2015; Rubia, Cubillo, et al., 2010; Rubia, Halari, Mohammad, Taylor, & Brammer, 2011; Rubia et al., 2008; Rubia et al., 1999; Rubia, Smith, Brammer, Toone, & Taylor, 2005), Go/No-Go (Booth et al., 2005; Durston, Mulder, Casey, Ziermans, & van Engeland, 2006;

Epstein et al., 2007), Stroop (Chou, Chia, Shang, & Gau, 2015), Simon (Rubia, Halari, Cubillo, et al., 2011) and switch tasks (Rubia, Cubillo, et al., 2010; Rubia, Halari, et al., 2010; Smith et al., 2006) in children and adolescents with ADHD relative to controls.

Studies of adults with ADHD have also revealed IFG underactivation in Stop (Congdon et al., 2014; Cubillo et al., 2010; Sebastian et al., 2012), Go/No-Go (Epstein et al., 2007), Stroop (Banich et al., 2009) Simon (Cubillo, Halari, Giampietro, Taylor, & Rubia, 2011) and switch tasks (Cubillo et al., 2010; Dibbets, Evers, Hurks, Bakker, & Jolles, 2010) relative to controls.

Underactivation of the IFG during inhibitory control has also been found to be shared between patients with ADHD and their unaffected first degree relatives (Durston et al., 2004; van Rooij, Hoekstra, et al., 2015), including in a large study of 185 adolescents an adult patients with ADHD, 112 unaffected siblings and 124 healthy controls during a Stop task (van Rooij, Hoekstra, et al., 2015). Disorder-specific underactivation in left IFG has been reported during Stop (Rubia et al., 2008) and Simon tasks (Rubia, Halari, Smith, et al., 2009) and in right IFG during switching (Rubia, Halari, et al., 2010) in adolescents with ADHD relative to adolescents with non-comorbid conduct disorder, as well as in left IFG during an emotional Stroop task (Passarotti, Sweeney, & Pavuluri, 2010a) and bilateral IFG during a Stop task (Passarotti, Sweeney, & Pavuluri, 2010b) relative to adolescents with bipolar disorder, and in right IFG during Stop and Switch tasks relative to adolescents with OCD (Rubia, Cubillo, et al., 2010).

Underactivation in the IFG during inhibitory control correlates with ADHD symptoms (Cubillo et al., 2010; Rubia et al., 2005; van Rooij, Hoekstra, et al., 2015), and impairments in task performance (Vaidya et al., 2005; van Rooij, Hoekstra, et al., 2015). IFG underactivation has been reported in meta-analyses of response inhibition, interference

inhibition and switching studies (Cortese et al., 2012; Hart et al., 2013; Lei, Du, et al., 2015; McCarthy, Skokauskas, & Frodl, 2014; Rubia, in press).

Together, these findings suggest that IFG underactivation during inhibitory control is a consistent finding in ADHD, which furthermore may be a neuroendophenotype associated with increased risk for the disorder, and a disorder-specific neurofunctional biomarker for ADHD relative to other childhood disorders (Rubia, in press; Rubia, Alegria, & Brinson, 2014; Rubia, Cubillo, et al., 2011). Clusters of underactivation in the IFG often extend into adjacent anterior insula, suggesting that impairments in both salience related and inhibition related brain networks in ADHD (Hart et al., 2013).

Consistent with fronto-striatal accounts of ADHD, in addition to underactivation in IFG, patients with ADHD show decreased recruitment of closely interconnected dorsal striatal regions including caudate and putamen during inhibitory control, as confirmed in recent meta-analyses (Hart et al., 2013; Lei, Du, et al., 2015; Rubia, in press). This has been reported in children and adolescents with ADHD during Stop (Hart, Chantiluke, et al., 2014; Rubia et al., 1999), Go/No-Go (Booth et al., 2005; Durston et al., 2003; Siniatchkin et al., 2012), Stroop (Peterson et al., 2009), Simon (Rubia, Halari, Cubillo, et al., 2011) and switching (Rubia, Cubillo, et al., 2010) tasks and in adults with ADHD during Stop (Cubillo et al., 2010; Sebastian et al., 2012), Go/No-Go (Epstein et al., 2007; Sebastian et al., 2012), Simon (Cubillo et al., 2011; Sebastian et al., 2012) and switching (Cubillo et al., 2010; Dibbets et al., 2010) tasks relative to controls. Dorsal striatum underactivation correlates with ADHD symptoms and poor performance during inhibitory control in ADHD (Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Rubia, Halari, Cubillo, et al., 2011).

Studies have also investigated abnormal functional connectivity in ADHD during inhibitory control (Cubillo et al., 2010; Hwang et al., 2015; van Rooij, Hartman, et al., 2015; Vloet,

Gilsbach, et al., 2010). Cubillo et al (2010) found reduced functional connectivity during a Stop task between right IFG and left IFG, caudate, ACC, PCC and bilateral parietal lobe relative to controls in adults that were diagnosed with ADHD during childhood. Hwang and colleagues (2015) reported reduced connectivity between dorsal MPFC and right DLPFC, but increased connectivity between dorsal MPFC and left insula during a Stroop task in paediatric ADHD patients relative to controls. In a large study including both adolescent and adult ADHD patients, patients were found to show reduced connectivity between right IFG and putamen, but increased connectivity within DMN network regions the dorsal MPFC, vmOFC and precuneus during a Stop task relative to controls (van Rooij, Hartman, et al., 2015). Finally, Vloet et al (2010) used a spatial stimulus–response compatibility task which measures interference inhibition, finding reduced connectivity in ADHD patients between right IFG and right superior parietal cortex in children and adolescents with ADHD relative to controls. Overall, studies suggest reduced functional connectivity within IFG-centred networks involved in inhibitory control in paediatric and adult ADHD.

### 3.4. Function neuroimaging of inhibitory control in OCD

In OCD, the majority of neuroimaging studies of inhibitory control have examined adult patients. Consistent with reduced r/d MPFC/ACC GMV in OCD, underactivation of this region has been reported in OCD patients during Stop (Kang et al., 2013; Rubia, Cubillo, et al., 2010), Go/No-Go (Page et al., 2009; Pena-Garijo et al., 2011; Roth et al., 2007), Stroop (Hou et al., 2011; Nabeyama et al., 2008; Nakao et al., 2005), Simon (Marsh et al., 2014; Rubia, Cubillo, et al., 2011) and switch tasks (Gu et al., 2008; Han et al., 2011; Page et al., 2009).

Abnormalities in striatal activation have also been reported. This includes underactivation in the caudate and/or putamen during Stop (Kang et al., 2013; Woolley et al., 2008), Go/No-Go

(Page et al., 2009; Pena-Garijo et al., 2011), Stroop (Hou et al., 2011; Nakao et al., 2005), and switch tasks (Gu et al., 2008; Han et al., 2011; Morein-Zamir et al., 2016; Page et al., 2009), although increased striatal activation has also been reported during Stop (Morein-Zamir et al., 2016), Go/No-go (Maltby, Tolin, Worhunsky, O'Keefe, & Kiehl, 2005; Roth et al., 2007), Simon (Marsh et al., 2014) flanker (Fitzgerald et al., 2005; Yucel et al., 2007) and switch tasks (Remijnse et al., 2013), suggesting that atypical striatal functioning rather than consistent underactivation is a feature of OCD (Morein-Zamir et al., 2016).

Studies have also noted abnormalities in functional connectivity during inhibitory control tasks in OCD patients, particularly involving MPFC (Cocchi et al., 2012; Fitzgerald et al., 2010; Stern et al., 2011). During interference inhibition, paediatric OCD patients show enhanced functional connectivity between vmOFC and dorsal ACC (Fitzgerald et al., 2010), while adults with OCD have been shown to demonstrate increased connectivity between vmOFC and anterior insula (Stern et al., 2011), or between dACC and left DLPFC (Schlösser et al., 2010). Cocchi et al. (2012) reported that within a network consisting of bilateral anterior insula/IFG, r/d MPFC, middle anterior cinglate cortex (mACC), supplementary motor area (SMA), and PCC, OCD patients showed increased anterior insula/IFG connectivity but reduced dorsal MPFC connectivity during an interference control task. To date, one study has examined functional connectivity during response inhibition in OCD, finding altered connecivity between IFG and amydala during a Stop task in OCD patients and healthy first-degree relatives when compared with controls, which was interpreted as enhanced influence of a brain region involved in detecting behavioural salience over a key hub of prefrontal EF networks in OCD (van Velzen, Vriend, de Wit, & van den Heuvel, 2014)

### 3.5. Function neuroimaging of sustained attention in ADHD

Only a small number of studies have examined sustained attention in ADHD using fMRI. The majority of these have used the CPT-AX task, finding reduced activation relative to controls in IFG, anterior insula, caudate, putamen, temporal, parietal, and cerebellar regions in both adolescents (Rubia, Smith, et al., 2009) and adults with ADHD (Cubillo, Halari, Smith, Taylor, & Rubia, 2012). Reduced connectivity between left and right IFG and caudate, putamen, thalamus and cerebellum, and as well as between the cerebellum and inferior parietal cortices, caudate, putamen, ACC, and PCC was also reported in ADHD patients relative to controls (Cubillo et al., 2012; Rubia, Halari, Cubillo, et al., 2009a). Reduced activation in IFG was disorder-specific to children with ADHD when compared to children with conduct disorder, and correlated with increased omission errors (Rubia, Smith, et al., 2009). A study of younger children (aged 7-12 years), however, reported increased insula, cerebellar and DLPFC activation in ADHD patients relative to controls (Wang et al., 2013).

Two studies have also used simple target detection tasks with varying delays (Christakou, Murphy, et al., 2013; Metin et al., 2015). Christakou and colleagues used a parametrically modulated sustained attention/vigilance task wherein participants had to respond as quickly as possible to a visual stimulus (a timer counting up in milliseconds) after unpredictable delays of 2, 5, or 8 seconds. Adolescent patients with ADHD showed underactivation in left DLPFC and bilateral thalamus/putamen/hippocampus as well as decreased DMN deactivation in the precuneus relative to controls. Moreover, left DLPFC activation was significantly reduced relative to patients with autism spectrum disorder. In the study by Metin and colleagues, participants responded as quickly as possible to targets or ignored non-targets separated by delays of 2, 4, or 8 seconds. Functional MRI analysis focused on task-related DMN deactivation using ROI methods. Patients with ADHD showed reduced deactivation to

targets relative to non-targets than did controls during the 2 and 8 second trials. Failures to deactivate the DMN are proposed to underlie difficulties in sustained attention in ADHD, and in line with this hypothesis, numerous resting-state functional connectivity studies have reported altered DMN connectivity in ADHD rest (Choi, Jeong, Lee, & Go, 2013; Hoekzema et al., 2014; McCarthy et al., 2013; Sripada, Kessler, Fang, et al., 2014; Sun et al., 2012).

Also relevant for discussion are oddball tasks. Adolescents with ADHD show reduced recruitment in left IFG (Cubillo et al., 2011; Rubia, Halari, Smith, et al., 2009), which furthermore has been found to be disorder-specific relative to patients with conduct disorder (Rubia, Halari, Smith, et al., 2009). Decreased activation has also been reported in the striatum (Cubillo et al., 2011; Rubia, Cubillo, et al., 2011; Rubia, Smith, Brammer, et al., 2007), which was disorder-specific relative to adolescents with OCD (Rubia, Cubillo, et al., 2011), as well as in anterior insula (Rubia, Halari, Smith, et al., 2009; Rubia, Smith, Brammer, et al., 2007), temporal lobe (Rubia, Smith, Brammer, et al., 2007), precuneus/PCC and DLPFC (Cubillo et al., 2011; Rubia, Halari, Smith, et al., 2009). Whole-brain regressions with ADHD symptoms report significant negative correlations with right IFG, ACC, right inferior parietal cortex, PCC, cerebellum and striatum activation in ADHD patients (Cubillo et al., 2011; Rubia, Smith, Brammer, et al., 2007). Increased response time variability has been found to correlate with decreased activation in striatum, thalamus, left superior temporal lobe, and right cerebellum (Rubia, Smith, Brammer, et al., 2007).

### 3.6. Function neuroimaging of sustained attention in OCD

To date, no published studies have compared OCD patients with controls during sustained attention performance using fMRI. Only one study has used an explicitly attention related task during fMRI with OCD adolescents, finding during an oddball task that adolescents with OCD showed underactivation in right DLPFC relative to controls and adolescents with

ADHD. There was also a trend increase in right PCC and caudate activation which correlated positively with obsessive symptoms (Rubia, Cubillo, et al., 2011).

In a study of OCD adults using an attentional switching paradigm, participants were instructed to either direct their attention inwards by imagining positive or negative scenarios, or to direct their attention outwards by completing trials of a Stroop task. Following 12-18 second blocks of the imagination or Stroop tasks, participants completed a 15 second block of a target detection task. It was found that patients show decreased dorsal attention and salience network regions in superior and inferior occipital cortex, thalamus, and putamen and increased DMN connectivity during target detection following instructions to direct attention inwards towards imagining negative social events compared with controls (Stern et al., in press). Deficits in exteroceptive attention in OCD are proposed to result from failures to deactivate DMN regions and engage task-positive attention networks (Stern et al., in press)

### 3.7. Function neuroimaging of reward-related decision-making in ADHD

A small number of studies have used fMRI to examine neural abnormalities during TD in ADHD (Carlisi et al., 2016; Chantiluke et al., 2014; Ortiz et al., 2015; Plichta et al., 2009; Rubia, Halari, Christakou, et al., 2009). First, in studies of adolescents comparing neural activation during delayed and immediate responses underactivation during delayed choices has been reported in bilateral IFG and left OFC, putamen, thalamus, inferior parietal lobe, posterior cingulate, precuneus and cerebellum (Rubia, Halari, Christakou, et al., 2009), and in right pre- and post-central gyri, inferior parietal lobe and anterior insula (Carlisi et al., 2016). Furthermore, adolescents with ADHD showed significantly weaker correlations between better TD performance and activation during delayed choices in SMA, left IFG and superior temporal lobes, and right anterior insula, putamen and cerebellum (Chantiluke et al., 2014). In the first study of ADHD adults using fMRI during TD, Plitcha and colleagues (2009) used

ROI methods to examine striatal and limbic responses to choices involving an immediate and a delayed option and trials involving two delayed options against fixation baseline. They found that the ventral striatum (VS) was underactive for all decisions versus baseline, whereas the caudate and amygdala were hyperactive during decisions involving only two delayed options, in ADHD patients relative to controls. A subsequent study by Ortiz and colleagues (2015) used whole brain methods to examine neural abnormalities for all decisions versus fixation baseline, reporting underactivation in ADHD adults relative to controls in bilateral DLPFC and cerebellum, left inferior temporal lobe and inferior parietal lobe, and right ACC, caudate, post-central gyrus and precuneus.

Only one study has used neuroimaging to study decision-making on the IGT in ADHD (Ernst, Kimes, et al., 2003). Ernst and colleagues (2003) used PET to study adults with ADHD and controls, finding reduced activity in ADHD patients in left insula, hippocampus and inferior temporal lobe and increased activity in ACC, left postcentral gyrus and right superior temporal lobe relative to controls, as well as correlations between ADHD symptoms and underactivation in ACC, vmOFC, PCC, left DLPFC/IFG and left inferior temporal lobe and between ADHD symptoms and overactivation in right DLPFC/IFG and insula during IGT relative to baseline. However, this study did not separate decision-making and outcome phases of the task, making interpretations of findings difficult.

### 3.8. Function neuroimaging of reward-related decision-making in OCD

To date, no published studies have examined the neural basis of TD or decision-making under ambiguity in OCD. Two studies have examined explicit risky decision-making in OCD (Admon et al., 2012; Luigjes et al., 2016). In Admon et al (2012), adults with OCD were more risk averse than healthy controls and showed greater amygdala activation during the outcome anticipation phase following risky choices and reduced VS activation during

outcome anticipation following safe choices, as well as reduced vmOFC-VS and dorsal ACC-amygdala functional connectivity, than did controls. In the study by Luigjes et al (2016), adult OCD patients and controls did not differ according to the number of risky choices and there were no differences in brain activation between groups during decision-making. However, risk aversion correlated positively with increased anterior insula and DLPFC activation during high-risk decisions in OCD, but correlated negatively with anterior insula activation in controls.

### 3.8 Additional cool EF functional neuroimaging findings in ADHD

In studies of working memory, patients with ADHD show decreased activation in DLPFC (Chantiluke, Barrett, Giampietro, Brammer, Simmons, & Rubia, 2015; Cubillo et al., 2014a; McCarthy et al., 2014; Valera et al., 2010).

During timing tasks, patients with ADHD show reduced activation primarily in IFG, anterior insula, DLPFC, inferior parietal lobe, striatum and cerebellum (Hart, Marquand, et al., 2014; Hart, Radua, Mataix-Cols, & Rubia, 2012; Noreika et al., 2013; Rubia, Halari, Christakou, et al., 2009).

### 3.9. Additional hot EF functional neuroimaging findings in ADHD

A number of studies have used the monetary incentive delay (MID) task to study reward anticipation and outcome anticipation processing in ADHD (Edel et al., 2013; Hoogman et al., 2011; Kappel et al., 2015; Plichta & Scheres, 2014; Plichta et al., 2009; Scheres, Milham, Knutson, & Castellanos, 2007; Stoy et al., 2011; Strohle et al., 2008; von Rhein et al., 2015). The majority of studies report reduced VS activation to cues predicting rewards in ADHD (Edel et al., 2013; Hoogman et al., 2011; Kappel et al., 2015; Plichta & Scheres, 2014; Plichta et al., 2009; Scheres et al., 2007; Stoy et al., 2011; Strohle et al., 2008). Some studies

have also reported increased activation in vmOFC and VS during reward outcome in this task in ADHD patients (Strohle et al., 2008; von Rhein et al., 2015). A meta-analysis of reward anticipation studies using a ROI of the VS in patients with ADHD versus controls during six MID and one TD study reported a medium effect size for reduction in VS activation. These findings are interpreted as a failure to transfer phasic dopamine firing from reward outcomes to cues which predict reward, suggesting that impairments in reinforcement learning underlie motivation deficits when pursuing long-term goals and rewards in ADHD (Plichta & Scheres, 2014; Tripp & Wickens, 2008; Tripp & Wickens, 2009).

Studies have also provided a more direct examination of reward learning in ADHD (Furukawa et al., 2014). Using a classical conditioning paradigm, Furukawa and colleagues (2014) found that patients with ADHD showed decreased activation in VS to cues predicting rewards, but increased VS to reward outcomes. During a reward reversal task, adolescent patients with ADHD were found to show decreased activation in the precuneus during the final reversal error before a correct response (Chantiluke, Barrett, Giampietro, Brammer, Simmons, Murphy, et al., 2015). In reversal learning study by Hauser and colleagues (2014), adolescents with ADHD showed decreased sensitivity to reward prediction errors than controls in rostral MPFC during both cue and outcome presentation.

### 3.10. Additional cool EF functional neuroimaging findings in OCD

During working memory tasks, adolescents and adults with OCD show increased DLPFC, dorsal ACC, and parietal lobe activation than healthy controls (de Vries et al., 2014; Diwadkar et al., 2015)

Adolescent patients with OCD show decreased DLPFC and parietal lobe activation during planning (Huyser, Veltman, Wolters, de Haan, & Boer, 2010), while adults have been found

to show decreased DLPFC, dorsal ACC, parietal lobe and striatum activation (van den Heuvel et al., 2003).

In a study using PET, OCD adults showed reduced VS relative to controls during implicit sequence learning, and instead activated the hippocampus (Rauch et al., 1997). In a follow-up study using fMRI, patients with OCD showed increased hippocampal and vmOFC activation relative to controls, while reduced VS activation was associated with increased symmetry/ordering and washing/contamination symptoms (Rauch et al., 2007).

Studies have also examined the neural basis of heightened subjective and intolerance of uncertainty in OCD (Rotge et al., 2015; Stern et al., 2013). In Stern el al (2013), participants viewed red and blue cards being picked from one of two decks of cards. Each deck had a different proportion of red and blue cards, and participants had to decide which deck the cards were being drawn from. On certain trials, where one deck had only red and the other only blue cards, patients with OCD rated themselves as subjectively more uncertain of the correct deck and failed to deactivate the DMN in vmOFC, parahippocampus, amygdala and middle temporal lobe.

In a study of intolerance of uncertainty, Rotge and colleagues (2015) had patients and control perform a delayed matching-to-sample task with unrestricted opportunities to check a decision by repeating a trial. Greater self-reported intolerance of uncertainty was associated with increased checking and OFC activation in both the patient group and controls.

### 3.11. Additional "hot EF" functional neuroimaging findings in OCD

Patients with OCD show altered orbito-striato-limbic activation during emotional learning. Tasks involving flexible updating of reward and punishment contingencies find reduced lateral OFC and vmOFC activation in adult OCD patients following contingency change, as

has been reported in reward-reversal tasks, as well as during fear learning, extinction learning and extinction retrieval (Chamberlain et al., 2008; Freyer et al., 2011; Milad et al., 2013; Remijnse, Nielen, Balkom, et al., 2006; Remijnse et al., 2009).. Moreover, adult patients with OCD show reduced VS activation to cues which predict reward, or which no longer predict aversive outcomes, perhaps suggesting deficiencies in mesolimbic reinforcement learning (Figee et al., 2013; Figee et al., 2011; Marsh et al., 2015; Milad et al., 2013). Together these findings suggest underlying alterations in orbito-striatal networks responsible for updating stimulus-outcome associations. Abnormal functioning in this network may underlie continued misattributed salience to symptom provoking stimuli, despite negative evidence for expected feared outcomes, as well as a failure to attribute appropriate motivational salience to goal-relevant stimuli and behaviours (Gillan & Robbins, 2014; Milad et al., 2013; Milad & Rauch, 2012).

Relatedly, patients with OCD show increased vmOFC activation during an instrumental fear avoidance task relative to controls, although in controls activity increased over the course of the task, whereas in OCD patients it decreased. Moreover, OCD patients who continued to respond to the fear conditioned stimulus following devaluation showed increased activation in the caudate/VS (Gillan et al., 2015). These findings are interesting in light of the reliable finding that, during symptom provocation, patients with OCD show abnormal activation in similar vmOFC and striatal brain regions (Baioui et al., 2013; Banca et al., 2015; Breiter et al., 1996; Brennan et al., 2015; Mataix-Cols et al., 2004; Schienle, Schäfer, Stark, Walter, & Vaitl, 2005; Simon, Adler, Kaufmann, & Kathmann, 2014; van den Heuvel et al., 2009), and are in line with accounts suggesting that striatal hyperactivation in OCD represents enhanced influence of salience, motivation, and habit-learning networks, which are important for bottom-up behavioural control and may bias action-selection towards compulsive behaviours (Gillan et al., 2011; Gillan & Robbins, 2014; van den Heuvel et al., 2016).

### 3.12. Chapter summary

Both disorders show functional and structural abnormalities in primarily fronto-striatal brain networks that support inhibitory control, sustained attention and reward-related decision-making. However, the specific-patterns of abnormalities in the brain regions may be largely disorder-specific.

First, in the prefrontal cortex, the primary site of functional and structural abnormalities appears to be the IFG in ADHD (Rubia, in press; Rubia, Alegria, & Brinson, 2014). This region is underactive during inhibitory control, sustained attention, attention allocation, decision-making and timing tasks relative to controls (Banich et al., 2009; Booth et al., 2005; Chou et al., 2015; Congdon et al., 2014; Cortese et al., 2012; Cubillo et al., 2010; Cubillo et al., 2011; Cubillo et al., 2012; Cubillo et al., 2014b; Dibbets et al., 2010; Durston et al., 2004; Durston et al., 2006; Epstein et al., 2007; Hart, Chantiluke, et al., 2014; Hart et al., 2012; Hart et al., 2013; Janssen et al., 2015; Lei, Du, et al., 2015; McCarthy et al., 2014; Noreika et al., 2013; Rubia, in press; Rubia, Cubillo, et al., 2010; Rubia, Cubillo, et al., 2011; Rubia, Halari, Christakou, et al., 2009; Rubia, Halari, Cubillo, et al., 2009a; Rubia, Halari, et al., 2010; Rubia, Halari, Mohammad, et al., 2011; Rubia, Halari, Smith, et al., 2009; Rubia et al., 2008; Rubia et al., 1999; Rubia et al., 2005; Rubia, Smith, et al., 2009; Sebastian et al., 2012; Smith et al., 2006; van Rooij, Hoekstra, et al., 2015), and underactivation and decreased GMV in the IFG is shared with unaffected first-degree relatives of ADHD patients (Durston et al., 2004; Pironti et al., 2014). Disorder-specificity has been shown in patients with ADHD patients relative to OCD, bipolar disorder and conduct disorder patients during inhibitory control (Passarotti et al., 2010a, 2010b; Rubia, Cubillo, et al., 2010; Rubia, Halari, et al., 2010; Rubia, Halari, Smith, et al., 2009; Rubia et al., 2008), as well as relative to conduct disorder patients during sustained attention and attention allocation tasks (Rubia, Halari,

Smith, et al., 2009; Rubia, Smith, et al., 2009). Decreased GMV in this brain region correlates with impaired inhibitory control and sustained attention performance (Casey et al., 1997; Depue et al., 2010; Pironti et al., 2014).

In contrast, medial prefrontal regions including r/d MPFC/ACC and vmOFC appear to be the most affected in OCD. Decreased GMV has been reported in meta-analyses of VBM studies of OCD patients (Peng et al., 2012; Radua & Mataix-Cols, 2009; Radua et al., 2010), to be shared with their unaffected first degree relatives (Menzies et al., 2007), and to predict poor task performance during inhibitory control (Menzies et al., 2007). Underactivation in the r/d MPFC/ACC is also a consistent finding during inhibitory control tasks in OCD (Gu et al., 2008; Han et al., 2011; Hou et al., 2011; Kang et al., 2013; Marsh et al., 2014; Nabeyama et al., 2008; Nakao et al., 2005; Page et al., 2009; Pena-Garijo et al., 2011; Roth et al., 2007; Rubia, Cubillo, et al., 2010; Rubia, Cubillo, et al., 2011), while vmOFC is underactive during "hot EF" tasks, particularly those requiring patients to flexibly update stimulus-outcome contingencies (Milad et al., 2013; Remijnse, Nielen, Balkom, et al., 2006; Remijnse et al., 2009), shows abnormal activation during symptom provocation (Banca et al., 2015; Mataix-Cols et al., 2004), is hyperactive at rest (Hou et al., 2012; Whiteside, Port, & Abramowitz, 2004; Zhu et al., 2016) and subject to deactivation failures during cognitive task performance (Page *et al.* 2009; Stern et al. 2011; Stern et al. 2013; Agam et al. 2014; Brennan *et al.* 2015).

Structural and functional abnormalities in ADHD and OCD are also important in both disorders. In ADHD, decreased GMV in caudate and putamen has been reported in both adolescents and adults with the disorder (Anqi Qiu et al., 2009; Castellanos et al., 1996; Ellison-Wright et al., 2008; Filipek et al., 1997; Frodl & Skokauskas, 2012; Lim et al., 2013; Montes et al., 2011; Nakao et al., 2011; Onnink et al., 2014; Proal et al., 2011; Roman-Urrestarazu et al., 2016; Sobel et al., 2010; Valera et al., 2007; van Wingen et al., 2013), while adolescents and adults with OCD show enlarged caudate and putamen (Gilbert,

Keshavan, et al., 2008; Hou et al., 2013; Menzies et al., 2007; Narayanaswamy et al., 2013; Peng et al., 2012; Pujol et al., 2004; Radua & Mataix-Cols, 2009; Radua et al., 2010; Real et al., 2016; Subira et al., 2013; Szeszko et al., 2008; Tang et al., 2013; Yoo et al., 2008; Zarei et al., 2011), and reduced striatal GMV correlates with impaired inhibitory control in ADHD (Casey et al., 1997; McAlonan et al., 2009), whereas increased striatal GMV correlates with impaired inhibitory control in OCD (Menzies et al., 2007). Decreased dorsal striatal activation is reliably reported in inhibition, attention, temporal-discounting and timing tasks in ADHD (Booth et al., 2005; Carlisi et al., 2016; Christakou, Murphy, et al., 2013; Cortese et al., 2012; Cubillo et al., 2010; Cubillo et al., 2011; Dibbets et al., 2010; Durston et al., 2003; Epstein et al., 2007; Hart, Chantiluke, et al., 2014; Hart, Marquand, et al., 2014; Hart et al., 2012; Hart et al., 2013; Lei, Du, et al., 2015; McCarthy et al., 2014; Noreika et al., 2013; Peterson et al., 2009; Rubia, in press; Rubia, Cubillo, et al., 2010; Rubia, Cubillo, et al., 2011; Rubia, Halari, Christakou, et al., 2009; Rubia, Halari, Cubillo, et al., 2011; Rubia et al., 1999; Rubia, Smith, Brammer, et al., 2007; Sebastian et al., 2012; Siniatchkin et al., 2012). OCD patients have shown decreased GMV in dorsal striatal activation relative to controls during inhibition, attention and planning tasks (Gu et al., 2008; Han et al., 2011; Hou et al., 2011; Kang et al., 2013; Morein-Zamir et al., 2016; Nakao et al., 2005; Page et al., 2009; Pena-Garijo et al., 2011; van den Heuvel, Veltman, Groenewegen, Cath, et al., 2005; Woolley et al., 2008), although increased activation has also been reported, particularly in the putamen (Fitzgerald et al., 2005; Maltby et al., 2005; Marsh et al., 2014; Morein-Zamir et al., 2016; Remijnse et al., 2013; Roth et al., 2007; Yucel et al., 2007). Increased striatal activation is also a common finding during symptom provocation and at rest in OCD (Baioui et al., 2013; Banca et al., 2015; Breiter et al., 1996; Brennan et al., 2015; Mataix-Cols et al., 2004; Simon et al., 2014; van den Heuvel et al., 2009; Whiteside et al., 2004).

However, ADHD and OCD patients may share dysfunction in the VS. Both patient groups show decreased VS activation during learning tasks (Furukawa et al., 2014; Marsh et al., 2015; Rauch et al., 1997; Remijnse, Nielen, Balkom, et al., 2006; Remijnse et al., 2009), and decreased VS activation to cues that predict rewards in the MID (Edel et al., 2013; Figee et al., 2013; Figee et al., 2011; Hoogman et al., 2011; Kappel et al., 2015; Plichta & Scheres, 2014; Plichta et al., 2009; Scheres et al., 2007; Stoy et al., 2011; Strohle et al., 2008), suggesting shared abnormalities in dopaminergic mesolimbic reinforcement learning pathways.

Both disorders also show altered connectivity within the DMN or between the DMN and task-positive networks at rest (Beucke et al., 2014; Choi et al., 2013; Hoekzema et al., 2014; Hou et al., 2013; McCarthy et al., 2013; Shin, Jung, et al., 2014; Sripada, Kessler, Fang, et al., 2014; Stern et al., 2012; Sun et al., 2012), as well as enhanced activation or decreased deactivation within DMN regions including the PCC/precuneus and MPFC during cognitive tasks (Agam et al., 2014; Christakou, Murphy, et al., 2013; Cubillo et al., 2012; Durston et al., 2003; Fassbender et al., 2009; Gu et al., 2008; Kang et al., 2013; Liddle et al., 2011; Metin et al., 2015; Page et al., 2009; Peterson et al., 2009; Roth et al., 2007; Rubia, Smith, et al., 2009; Stern et al., 2011; van den Heuvel, Veltman, Groenewegen, Witter, et al., 2005; Yucel et al., 2007; Zhu et al., 2016), and failures of deactivation in the DMN are proposed to underlie problems with sustained attention and excessive mind-wandering in both ADHD and OCD (Liu, Bilek, & Fitzgerald, 2016; Sonuga-Barke & Castellanos, 2007; Stern et al., 2012).

There are only a handful of functional neuroimaging studies in adolescents with OCD (Britton et al., 2010; Diwadkar et al., 2015; Huyser et al., 2010; Huyser, Veltman, Wolters, de Haan, & Boer, 2011; Rubia, Cubillo, et al., 2010; Rubia, Cubillo, et al., 2011; Woolley et al., 2008), and most have used small sample sizes ($n<15$), and highly comorbid and/or mostly medicated patient samples.

Inhibitory control was the most studied EF in both disorders, and the only published direct comparisons of ADHD and OCD using fMRI have used inhibitory control tasks, finding disorder-specific underactivation in ADHD adolescents relative to OCD adolescents in right IFG during switch and stop tasks, and in the dorsal striatum during switch and in the oddball contrast from a Simon task (Rubia, Cubillo, et al., 2010; Rubia, Cubillo, et al., 2011).

Only a handful of studies have examined sustained attention and TD in ADHD, and there are no published fMRI studies in OCD using these tasks. Despite evidence for performance deficits in both ADHD and OCD during the IGT (Chapter 2), there are no published studies in either disorder using fMRI. Moreover, there are no existing fMRI studies of reward related decision-making in OCD youth.

## Chapter 4. Design and aims of the current study

As reviewed in chapters 1-3, both ADHD and OCD patients share performance deficits in inhibitory control, sustained attention, and reward-related decision-making, as well as abnormalities in underlying prefrontal and dorsal striatal networks implicated in inhibitory control and temporal foresight, the DMN which may underlie poor performance during sustained attention, and in mesolimbic pathways important for decision-making and processing rewards and punishments.

However, the extent to which inhibitory control, sustained attention and decision-making performance are associated with shared or disorder-specific patterns of underlying neural abnormalities is unclear. Shared abnormalities would support the idea that these cognitive deficits tap into similar underlying mechanisms in both disorders, whereas largely disorder-specific findings would suggest that shared performance deficits represent distinct phenocopies. It is the aim of the current thesis to investigate this research question, by first conducting a comparative multi-modal meta-analysis of VBM studies of GMV and fMRI studies of inhibitory control in ADHD and OCD, and then by comparing brain activation in adolescents with ADHD, adolescents with OCD and healthy control adolescents during performance on (i) sustained attention (ii) TD and (iii) IGT paradigms using fMRI.

Most previous neuroimaging studies in OCD have investigated adult samples, and those which have looked at OCD in children and adolescents have tended to use highly comorbid (Fitzgerald et al., 2010; Huyser et al., 2010; Huyser et al., 2011) or largely medicated (Britton et al., 2010; Fitzgerald et al., 2010; Huyser et al., 2010; Huyser et al., 2011; Rubia, Cubillo, et al., 2010; Rubia, Cubillo, et al., 2011; Woolley et al., 2008) samples. The currently proposed research would therefore contribute to the field by examining neural abnormalities associated with OCD, without the confounding effects of comorbid disorders, long-term symptom

exposure, and medication exposure on neural structure and function.

Moreover, no studies have yet investigated neural functioning during tasks of sustained attention and reward-based decision-making in adolescents with OCD. Deficits in performance during these task domains are consistent findings in OCD populations (Chapter 2), and therefore the current project will provide an important investigation of the neural mechanisms which underlie these deficits.

Most importantly, only two published studies have directly compared patients with ADHD and OCD on neural functioning (Rubia, Cubillo, et al., 2010; Rubia, Cubillo, et al., 2011), and no published work has examined shared and disorder specific abnormalities in GMV in these disorders. Examining the extent to which ADHD and OCD share neural abnormalities has important implications for our understanding of the mechanisms that underlie symptomatology in both disorders, and the extent to which inhibitory control, sustained attention and reward-related decision-making represent true transdianostic phenotypes in ADHD and OCD.

### 4.1. Multi-modal meta-analysis

There are a large number of studies which have examined neural alterations associated with inhibitory control performance in ADHD and OCD, including the only published direct fMRI comparisons of ADHD and OCD neural dysfunction (Rubia, Cubillo, et al., 2010; Rubia, Cubillo, et al., 2011). Moreover, there exists a large VBM literature of GMV abnormalities in ADHD and OCD (Chapter 3).

Therefore, an aim of this PhD was to use Anisotropic Effect-Size Seed-based *d* Mapping (AES-SDM) to conduct a multimodal comparative meta-analysis of the existing ADHD and OCD VBM and fMRI of inhibitory control literature (Radua & Mataix-Cols, 2009; Radua et

al., 2012; Radua, Romeo, Mataix-Cols, & Fusar-Poli, 2013; Radua et al., 2014; Radua et al., 2010). AES-SDM uses an anisotropic non-normalized Gaussian kernel to recreate an effect-size map and an effect-size variance map for the contrast between patients and controls from peak coordinates and effect-sizes, for each individual VBM or fMRI study. Following this, mean maps of regional GMV and activation abnormalities within each patient group relative to controls is created by performing a voxel-wise calculation of the random-effects mean of the study maps, weighted by sample size and variance of each study and between-study heterogeneity. Importantly, AES-SDM allows quantitative comparisons to be performed of abnormalities (relative to controls) in GMV and functional activation between ADHD and OCD by calculating the difference between each patient group in each voxel, and then using standard randomization tests to establish statistical significance (Radua et al., 2010). AES-SDM software further allows for conjunction/disjunction analyses of shared/contrasting abnormalities across both patient groups relative to controls and across imaging modalities with each patient group, by computing the union of the p-values for each patient group within each voxel while accounting for noise in the estimation of meta-analytic p-values (Radua et al., 2013). Finally, the AES-SDM method allows for meta-regressions to be performed within each patient group for the effects of medication history (Radua & Mataix-Cols, 2009).

This meta-analysis therefore provides an examination of significant differences in structural and functional brain abnormalities relative to controls in ADHD and OCD, as well as an examination of regions where patient groups show overlapping shared or contrasting abnormalities. The meta-analysis will also examine overlapping multimodal structural and functional abnormalities within each disorder relative to controls.

## 4.2. fMRI study of the comparison between ADHD and OCD in tasks of attention and reward-based decision-making

### 4.2.2. Participant selection

Inclusion and exclusion criteria are depicted in Table 4.1.

Participants were right handed male adolescents participated, aged between 11-18, and with an IQ>70, as measured by the Wechsler Abbreviated Scale of Intelligence-Revised (WASI-R) short form (Wechsler, 2008). Only boys were studied due to preponderance of males in adolescent ADHD and OCD samples, and to achieve greater homogeneity across participants and groups (Geller et al., 1998; Willcutt, 2012).

ADHD boys were recruited from local child and adolescent mental health services (CAMHS) and met DSM-IV criteria for inattentive/hyperactive-impulsive combined subtype, as assessed using the standardized Maudsley diagnostic interview (Goldberg & Murray, 2006), and scored above clinical cut-off on the Conner's Parent Rating Scale-Revised (CPRS-R) (Conners, Sitarenios, Parker, & Epstein, 1998) and the inattention/hyperactivity scale of the parent Strength and Difficulty Questionnaire (SDQ) (Goodman, 1997).

OCD boys were recruited from a national specialist clinic for child and adolescent OCD and local CAMHS and had and had clinical diagnoses of OCD, assessed according to 10th edition of the International Classification of Diseases (ICD-10) criteria and the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill et al., 1997).

All patients were determined to be free of comorbid conditions by a psychiatrist or clinical psychologist who had performed a recent clinical assessment.

Medication naïve patients were recruited preferentially. However, patients receiving psychostimulant medication (ADHD), SSRIs (OCD) or anti-psychotics (OCD) were

ultimately included due to difficulties in recruiting entirely medication naïve samples. ADHD patients withdrew from medication for 48 hours before taking part in the study, which is more than 10 times the half-life of stimulant medication. Due to the longer wash-out period required for SSRIs of 2-3 weeks, it was determined that it would be unethical for OCD patients to be asked to withdraw from taking medication for the scanning session.

**Table 4.1. Participant Recruitment Criteria.**

| | |
|---|---|
| Age | 11-18 |
| Gender | Male |
| Handedness | Right handed |
| IQ | > 70 |
| Exclusion Criteria | Co-morbid psychiatric condition (except conduct disorder in ADHD); head injury, epilepsy, or genetics associated with ASD (e.g.: TS/FX), neurological disorder, drug/alcohol dependency, IQ< 70, age <11 or >17, 11 months. |
| Medication History | Psychoactive medication-naïve, or psychostimulants (ADHD), SSRIs (OCD) or anti-psychotics (OCD). |
| Symptoms | Controls: No history of mental health diagnoses.<br>ADHD: DSM-IV diagnosis of inattentive/hyperactive-impulsive combined type ADHD. Scores $\geq$ 7 for ADHD symptoms on the SDQ.<br>OCD: DSM-IV diagnosis for OCD. Scores of $\geq$8 on the CYBOC. |

*Abbreviations*: ADHD, Attention Deficit Hyperactivity Disorder; CY-BOC, Children's Yale-Brown Obsessive Compulsive Scale; OCD, obsessive compulsive disorder; SDQ, Strength and Difficulties Questionnaire; SSRIs, selective serotonin re-uptake inhibitors.

### 4.2.3. Neuroimaging methods and design

Out of the neuroimaging techniques available, fMRI was selected for the purposes of this study. This was based on its superior spatial resolution relative to EEG/ERPs, fNIRS and PET, and its ability to study both subcortical in addition to cortical regions, which is important given that subcortical striatal regions are implicated heavily in ADHD and OCD. Functional MRI is non-invasive as it does not require injection of isotopes, and therefore this method was deemed safe and ethical for use in adolescent samples.

The majority of participants completed three task paradigms within a single session. These included the sustained attention task (SAT), TD task and IGT. Analyses focus on differences in brain activation between the healthy controls, ADHD patients and OCD patients in each of the three tasks, consequently allowing for a direct assessment of shared and disorder-specific brain abnormalities in paediatric ADHD and OCD.

### 4.3.4. Paradigms used

Both patient groups show performance deficits in during sustained attention, but no studies have investigated whether there are shared or distinct underlying neurocognitive mechanisms, and no previous work has investigated sustained attention in OCD using fMRI. In the SAT (Christakou, Murphy, et al., 2013; Murphy et al., 2014), participants respond to probes which are presented after either short predictable delays of 0.5s, or after unpredictable longer time delays of 2, 5 or 8 s. This task provides advantages over the CPT-AX task more commonly used in ADHD fMRI research, due to its reduced working memory component, which is important in light of working memory deficits in both disorders (Willcutt et al., 2005), as well as its parametric design, which allows for the study of brain regions that show increasing and decreasing activation with increasing levels of sustained attention load. The SAT has been shown to activate DLPFC, parietal lobe, cerebellum, striatum and insula in healthy children and adults and to elicit decreased DLPFC, parietal, and striatal activation and increased precuneus activation in ADHD adolescents relative to controls (Christakou, Murphy, et al., 2013; Murphy et al., 2014). This task therefore requires activation of task-positive attention and salience networks and deactivation of the DMN, and the interplay of these networks is hypothesised to underlie impairments in sustained attention in both disorders (Metin et al., 2015; Sonuga-Barke & Castellanos, 2007; Stern et al., in press).

In the TD task (Carlisi et al., 2016; Chantiluke et al., 2014; Christakou et al., 2011; Rubia, Halari, Christakou, et al., 2009), participants are presented with the choice of an amount of

money (£100) available after a delay or a smaller amount of money available immediately (0-£100). Delay lengths are one week, one month and one year. Previous research suggests that subjective reward values are a function of both magnitude and time delay, as participants often choose smaller immediate rewards over larger delayed ones (Hamilton et al., 2015; Scheres et al., 2013). For each participant, an algorithm is used to find values for the immediate option that are treated subjectively as equivalent to the larger delayed option for each delay length, thus ensuring each participant makes an equal number of immediate and delayed choices. Successful performance on this task requires that participants consider the longer-term consequences of their choices and forego immediate rewards in order to maximise long-term gains, a process known as temporal foresight (Christakou et al., 2011; Rubia, Halari, Christakou, et al., 2009). Impulsive decision-making is a feature of ADHD and OCD during TD (Jackson & MacKillop, 2016; Patros et al., 2016; Sohn et al., 2014), and TD performance depends on the interplay of lateral and medial fronto-striatal networks implicated in self-control/temporal foresight and reward processing/motivation, which are hypothesised to be impaired in paediatric ADHD and OCD (Menzies et al., 2008; Rubia, Alegria, & Brinson, 2014). The task has rarely been studied in ADHD adolescents using fMRI (Carlisi et al., 2016; Chantiluke et al., 2014; Rubia, Halari, Christakou, et al., 2009), and no previous published fMRI studies of TD performance in OCD patients are available in the literature.

In the IGT, participates learn that two decks are associated with large wins but even larger losses and two decks are associated with small wins but even smaller losses (Bechara et al., 1994; Bechara et al., 1999; Bechara et al., 1997; Christakou et al., 2009; Christakou, Gershman, et al., 2013). Functional MRI adapted versions of the IGT allow for the measurement of neural activation patterns associated with decision-making and win/loss feedback (Christakou et al., 2009; Christakou, Gershman, et al., 2013). Performance of the

IGT requires temporal foresight, as participants must inhibit choices to the more alluring "risky" decks, which offer the possibility of short-term gains (e.g., a large immediate win), but nonetheless provide poorer outcomes over a longer time frame (Christakou, Gershman, et al., 2013; Noreika et al., 2013). In addition, performance on the IGT requires strategic reward learning, as participants must learn and update expected outcomes for each of the decks (Christakou et al., 2009; Christakou, Gershman, et al., 2013). Impaired performance on the IGT is a highly replicable finding in both disorders (Abouzari et al., 2016; Agay et al., 2010; Baker, 2011; Cavedini et al., 2002; Cavedini et al., 2012; da Rocha et al., 2011; Dekkers et al., 2016; Ernst, Grant, et al., 2003; Garon et al., 2006; Grassi et al., 2015; Hobson et al., 2011; Kashyap et al., 2013; Kim et al., 2015; Kodaira et al., 2012; Malloy-Diniz et al., 2007; Malloy-Diniz et al., 2008; Mantyla et al., 2012; Martoni et al., 2015; Medrano et al., 2015; Miller et al., 2013; Starcke et al., 2009, 2010; Toplak et al., 2005; Zhang, Dong, Ji, Tao, et al., 2015; Zhang, Dong, Ji, Zhu, et al., 2015), but this task remains unstudied using fMRI in both ADHD and OCD. Both disorders are hypothesised to have deficits in mesolimbic brain circuitry responsible for emotional learning processes, which may mediate successful task performance on the IGT (Christakou et al., 2009; Christakou, Gershman, et al., 2013; Dunn, Dalgleish, & Lawrence, 2006; Furukawa et al., 2014; Gillan & Robbins, 2014; Tripp & Wickens, 2008; Tripp & Wickens, 2009). Moreover, both disorders are associated with abnormal processing of rewarding and punishing outcomes (Figee et al., 2011; Remijnse, Nielen, Balkom, et al., 2006; Remijnse et al., 2009; von Rhein et al., 2015), although the neural basis of these abnormalities have not been examined in OCD adolescents, and have not been quantitatively compared between ADHD and OCD patient groups.

#### 4.3.4. Hypotheses

It was hypothesised that disorders would show both shared and disorder-specific patterns of brain abnormalities. In the meta-analysis, disorder-contrasting abnormalities in the basal

ganglia were anticipated. Reduced basal ganglia GMV was expected in ADHD, whereas enhanced GMV was anticipated in OCD. Underactivation of the IFG during inhibitory control was expected to be greater in or disorder-specific to ADHD relative to OCD. Greater or disorder-specific MPFC GMV and activation abnormalities during inhibitory control were expected in OCD relative to ADHD.

During sustained attention, it was hypothesised that both disorders would show reduced activation in task-positive salience and executive attention networks, and decreased deactivation of the DMN relative to controls (Christakou, Murphy, et al., 2013; Sonuga-Barke & Castellanos, 2007; Stern et al., in press; Stern et al., 2011; Stern et al., 2013), but that IFG underactivation would be more pronounced or disorder-specific to ADHD patients (Rubia, Alegria, & Brinson, 2014; Rubia, Cubillo, et al., 2010), while ventromedial prefrontal cortex hyperactivation would be more pronounced or disorder-specific in OCD relative to ADHD patients (Agam et al., 2014; Brennan et al., 2015; Page et al., 2009; Stern et al., 2011; Stern et al., 2013).

During TD and IGT, it was anticipated that patients with ADHD would show greater or disorder-specific impairments in IFG, and patients with OCD would show greater or disorder-specific impairments in vmOFC. During outcome processing in the IGT, patients with OCD were expected to show reduced striato-limbic responses to reward, whereas patients with ADHD were hypothesised show enhanced striato-limbic responses to reward.

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# Chapter 6. Shared and disorder-specific task-positive and default mode network dysfunctions during sustained attention in paediatric Attention-Deficit/Hyperactivity Disorder and obsessive/compulsive disorder

## 6.1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) affects 3-8% of children worldwide and 4% of adults (Biederman et al., 2012), and is defined by age-inappropriate problems with inattention, impulsivity and hyperactivity (American Psychiatric Association 2013).

OCD has a lifetime risk of 2-3% (Ruscio et al., 2010). The key symptoms are obsessions, defined as recurrent and intrusive thoughts (e.g., on themes of contamination, checking, orderliness and symmetry), and compulsions, i.e. repetitive, ego-dystonic and time-consuming behavioural and mental rituals (e.g., repetitive washing or checking) (American Psychiatric Association 2013).

Sustained attention refers to the ability to voluntarily maintain the focus of attention for infrequently occurring critical events (Parasuraman et al., 1998; Warm, 1984). Neurally, it is dependent on the interplay of four canonical brain networks (Menon, 2011; Metin et al., 2015). First is the "task-positive" central executive network (CEN) consisting of DLPFC, IFG, lateral parietal, and dorsal striato-thalamic regions, which is engaged during tasks requiring the active maintenance of attention toward external stimuli, mediates goal-directed selection of stimuli and responses, and is associated with adaptive performance on sustained attention tasks (Dosenbach et al., 2007; Petersen & Posner, 2012). The task-positive ventral attention network (VAN), consisting of IFG and the temporo-parietal junction (TPJ), and the salience network (SN), consisting of anterior insula and middle/dorsal anterior cingulate cortex (mACC/dACC), are involved in detecting behaviourally relevant cues, and engage the

CEN and disengage the DMN according to perceived environmental demands (Cai, Ryali, Chen, Li, & Menon, 2014; Menon, 2011; Seeley et al., 2007). The "task-negative" DMN consists of anterior/ventromedial prefrontal cortex (A/VMPFC), ACC, PCC, precuneus, and inferior temporal regions which are proposed to mediate internally generated cognition such as mind-wandering and rumination (Buckner, Andrews-Hanna, & Schacter, 2008). This network is typically deactivated during cognitive tasks (Raichle, 2015; Raichle et al., 2001). Activation in task-positive networks is typically anti-correlated with that in DMN, and a failure to adequately disengage DMN is associated with poorer sustained attention performance, presumably due to an increase of self-referential thoughts at the expense of exteroceptive goal-directed attention (Christakou, Murphy, et al., 2013; Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Rubia, in press).

Sustained attention has been found to be impaired in ADHD (Huang-Pollock et al., 2012; Losier et al., 1996; Malloy-Diniz et al., 2007; Mowinckel et al., 2015; Rubia, Halari, Cubillo, et al., 2009b; Rubia, Smith, & Taylor, 2007; Willcutt et al., 2005) and OCD (Abramovitch et al., 2013; Baykal et al., 2014; Benzina, Mallet, Burguière, N'Diaye, & Pelissolo, 2016; Bersani et al., 2013; Morein-Zamir, Craig, et al., 2010; Rajender et al., 2011; Snyder et al., 2015; Trivedi et al., 2008), and both ADHD and OCD patients self-report impaired executive attention abilities (Armstrong et al., 2011; Benatti et al., 2014; Grassi et al., 2015; Malloy-Diniz et al., 2007; Nandagopal et al., 2011; Sohn et al., 2014). Both disorders have been linked to increased spontaneous mind-wandering (Mowlem et al., 2016; Seli et al., 2016; Seli et al., 2015), which is proposed to reflect an imbalance between CEN, VAN, SN and the DMN (Christakou, Murphy, et al., 2013; Metin et al., 2015), and to underlie poor performance on sustained attention tasks, as attention is focused on internal thoughts, therefore limiting attention resources available for task-relevant processing (Thomson, Besner, & Smilek, 2015).

In ADHD, poor concentration is a symptom of the disorder (American Psychiatric Association, 2013) associated in particular with poor educational and workplace performance (Todd et al., 2002), and sustained attention deficits are one of the most consistent neuropsychological findings (Huang-Pollock et al., 2012). In OCD, difficulty in sustaining attention towards external goal-relevant stimuli is a plausible neurocognitive mechanism which may underlie difficulties in disengaging from internally generated obsessional thoughts, which are hypothesised to be mediated by DMN (Seli et al., 2016; Stern et al., in press). Shared behavioural deficits in sustained attention could suggest a transdiagnostic mechanism, which may underlie distinct symptomatology in each disorder. However, the extent to which sustained attention performance is associated with shared and disorder-specific neural dysfunctions in ADHD and OCD is unknown. Shared neural dysfunction during sustained attention would suggest a transdiagnostic mechanism in ADHD and OCD, while largely distinct neural abnormalities would suggest that shared sustained attention deficits are phenocopies with disorder-specific underlying neural mechanisms.

ADHD patients show reduced recruitment in SN (insula), VAN (IFG) and CEN (IFG/DLPFC/striatum/cerebellum) regions and increased DMN (ACC/PCC/precuneus) activation during attention tasks (Christakou, Murphy, et al., 2013; Cubillo et al., 2012; Hart et al., 2013; Metin et al., 2015; Rubia, Halari, Cubillo, et al., 2009a; Rubia, Smith, et al., 2009). The IFG, in particular, is a key region in ADHD which has been shown to be reliably underactive across multiple tasks of cognitive and attention control (Cortese et al., 2012; Hart et al., 2012; Hart et al., 2013; Lei, Du, et al., 2015; Rubia, in press). It has been found to be disorder-specific relative to OCD (Rubia, Cubillo, et al., 2010), as confirmed in a meta-analytic comparison of 489 ADHD and 287 OCD patients during inhibitory control tasks (Chapter 5), as well as relative to bipolar disorder (Passarotti et al., 2010a, 2010b) and

conduct disorder (Rubia, 2011; Rubia, Halari, et al., 2010; Rubia, Halari, Smith, et al., 2009; Rubia, Smith, et al., 2009) during cognitive control and attention tasks.

To our knowledge, no previous fMRI studies of sustained or focused attention in OCD have yet been published. However, it has been shown that patients with OCD demonstrate abnormalities in CEN, DMN and SN connectivity at rest (Stern et al., 2012; Zhu et al., 2016).

The A/VMPFC is a key DMN region typically deactivated during cognitive tasks (Raichle, 2015). Increased A/VMPFC activation has been reported in OCD at rest (Menzies et al., 2008; Zhu et al., 2016), during symptom provocation (Brennan et al., 2015; Rotge et al., 2009) and during cognitive tasks (Agam et al., 2014; Brennan et al., 2015; Page et al., 2009; Stern et al., 2011; Stern et al., 2013) suggesting that OCD symptoms may be associated with a failure to adequately regulate activity in this DMN region (Agam et al., 2014; Stern et al., 2012; Stern et al., in press; Stern et al., 2011; Stern et al., 2013). Conventional treatment including CBT (Yamanishi et al., 2009) and SSRI treatment (Carey et al., 2004), as well as treatment with deep-brain stimulation (Le Jeune et al., 2010), and repetitive transcranial magnetic stimulation (Nauczyciel et al., 2014) normalize A/VMPFC activity in OCD, while fMRI neurofeedback training targeting this region has been shown to decrease OCD symptoms (Scheinost et al., 2013; Scheinost et al., 2014). Abnormalities have also been reported in SN, which is hyperactive to errors (Stern et al., 2011), emotional stimuli (Berlin et al., 2015), and during symptom provocation (Brennan et al., 2015), but shows decreased negative connectivity with DMN at rest (Stern et al., 2012). Finally, functional alterations in CEN regions such as DLPFC, dorsal striatum and cerebellum have been reported previously in OCD during cognitive tasks (Gu et al., 2008; Kang et al., 2013; Page et al., 2009; Woolley et al., 2008), and structural abnormalities in these regions are reliably found in OCD (Chapter 5) (de Wit et al., 2014).

In this study, the aim was to conduct a direct comparison of neurofunctional abnormalities in paediatric ADHD and OCD during a vigilance task that measures sustained attention. For this purpose, a parametrically modified vigilance task with three levels of vigilance load was used which has been shown to activate DLPFC, parietal lobe, cerebellum, striatum and insula in healthy children (Christakou, Murphy, et al., 2013; Murphy et al., 2014) and adults (Murphy et al., 2014) and to elicit decreased DLPFC, parietal, and striatal activation and increased precuneus activation in ADHD adolescents relative to controls (Christakou, Murphy, et al., 2013). It was hypothesised that both disorders would show reduced activation in SN, VAN and CEN regions, and decreased deactivation of the DMN regions relative to controls (Christakou, Murphy, et al., 2013; Sonuga-Barke & Castellanos, 2007; Stern et al., in press; Stern et al., 2011; Stern et al., 2013), but that IFG underactivation would be more pronounced or disorder-specific to ADHD patients (Rubia, Alegria, & Brinson, 2014; Rubia, Cubillo, et al., 2010), while A/VMPFC hyperactivation would be more pronounced or disorder-specific in OCD relative to ADHD patients (Agam et al., 2014; Brennan et al., 2015; Page et al., 2009; Stern et al., 2011; Stern et al., 2013).

## 6.2. Materials and methods

### 6.2.1. Participants

Sixty (20 ADHD, 20 OCD, 20 controls) right handed (Oldfield, 1971) male adolescents aged between 12-18 years participated, with an IQ>70 as measured by the WASI-R short form (Wechsler, 2008). ADHD boys were recruited from local CAMHS, met DSM-IV criteria for inattentive/hyperactive-impulsive combined subtype, as assessed using the standardized Maudsley diagnostic interview (Goldberg & Murray, 2006), and scored above clinical cut-off on the CPRS-R (Conners et al., 1998) and the inattention/hyperactivity scale of the parent SDQ (Goodman, 1997). Thirteen boys were medication naïve, while 7 were receiving psychostimulant medication. Medicated ADHD patients underwent a 48 hour washout period

prior to scanning. OCD boys had clinical diagnoses of OCD, assessed according to the ICD-10 criteria and the CY-BOCS (Scahill et al., 1997), and were recruited from a national specialist clinic for child and adolescent OCD and local CAMHS. Sixteen boys were medication naïve, while four were being treated with SSRI medication. Control participants had no diagnoses of any psychiatric conditions, and were recruited using local advertising.

Ethical approval was obtained from the local Research Ethics Committee (05/Q0706/275), and the study was conducted in accordance with the Declaration of Helsinki. Study details were explained to both child and guardian. Written informed consent was obtained for all participants.

### 6.2.2. Sustained attention task

The SAT (Christakou, Murphy, et al., 2013; Murphy et al., 2014) is a variant of psychomotor/vigilance and delay tasks (Drummond et al., 2005) and requires participants to respond with a right-handed button press as quickly as possible and within 1 second to a visual stimulus (a timer counting up in milliseconds). The timer appears after either short, predictable, consecutive delays of 0.5 seconds in series of three to five stimuli (240 trials total) or after unpredictable delays of 2, 5, or 8 seconds (20 trials each). Trials involving longer delays were pseudorandomly interspersed into the 0.5-second series after at least three short delay trials. The long, infrequent, unpredictable delays require greater sustained attention/vigilance, while the short, predictable 0.5 s delays are typically anticipated and therefore place a higher demand on sensorimotor synchronisation (Christakou, Murphy, et al., 2013; Murphy et al., 2014) (Figure 6.1.) Each participant practiced the task once in a mock scanner before scanning.

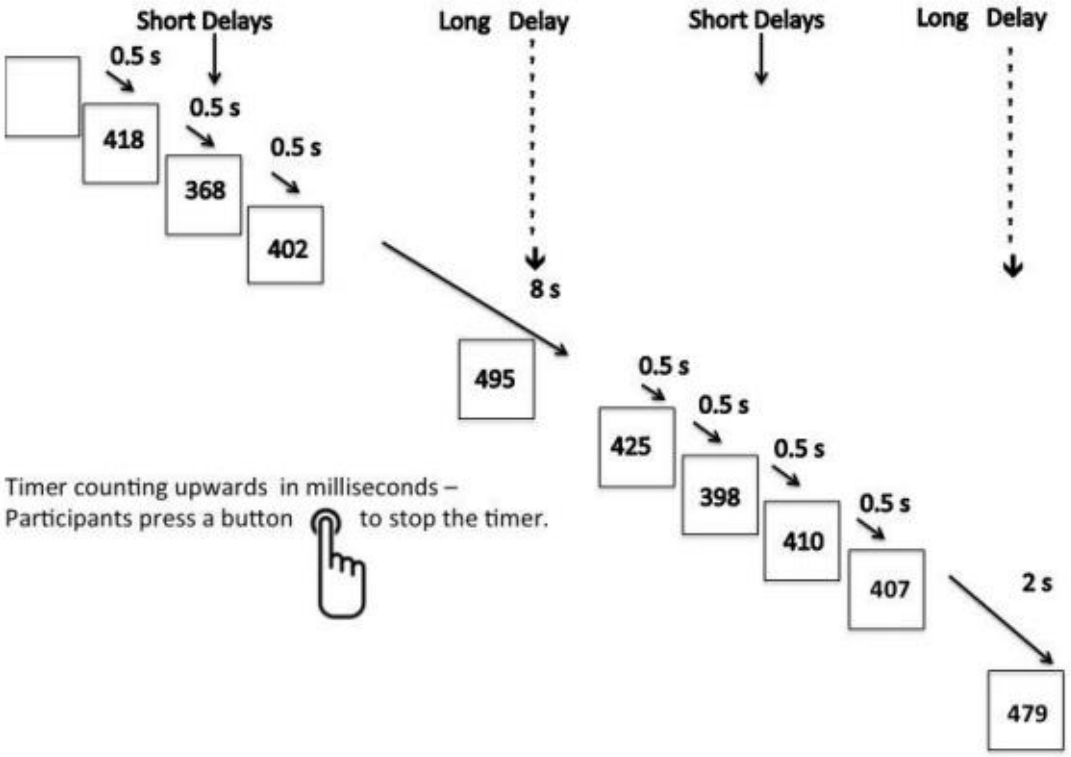



**Figure 6.1. Schematic representation of the Sustained Attention Task (SAT).** Participants are required to press a right-hand button as soon as they see a timer appear on the screen. The counter appears after either predictable short delays of 0.5 seconds in series of three to five trials or after unpredictable delays of 2, 5, or 8 seconds, which are pseudorandomly interspersed into the 0.5-second series after at least three short delay trials. The long, infrequent, unpredictable delays require greater sustained attention, while the predictable 0.5 s delays place a higher demand on sensorimotor synchronisation.

### 6.2.3. Analysis of Performance Data

To examine differences in performance, 3 (group) by 3 (delay) within-between repeated measures ANOVAs were used. The dependent variables were reaction time, reaction time variability and omission errors.

### 6.2.4. fMRI Image Acquisition

The fMRI images were acquired at King's College London, Institute of Psychiatry's Centre for Neuroimaging Sciences on a 3T General Electric Signa Horizon HDx MRI scanner (GE Healthcare, UK) using the body coil for radio frequency transmission and a quadrature birdcage headcoil for radio frequency transmission and reception. In each of 22 non-

contiguous planes parallel to the anterior–posterior commissure, 480 T2⁎-weighted MR images depicting BOLD (blood oxygen level dependent) contrast covering the whole brain were acquired with echo time (TE)=30 ms, repetition time (TR)=1.5 s, flip angle=60°, in-plane voxel size=3.75 mm, slice thickness=5.0 mm, slice skip=0.5 mm). A whole-brain high resolution structural scan (inversion recovery gradient echo planar image) used for standard space normalisation was also acquired in the inter-commissural plane with TE=40 ms, TR=3 s, flip angle=90°, number of slices: 43, slice thickness=3.0 mm, slice skip=0.3 mm, in-plane voxel size=1.875 mm, providing complete brain coverage.

### 6.2.5. fMRI Data Analysis Methods

Data were first processed to minimize motion-related artefacts (Bullmore, Brammer, et al., 1999). A 3-D volume consisting of the average intensity at each voxel over the entire experiment was calculated and used as a template. The 3D image volume at each time point was then realigned to this template by computing the combination of rotations (around the *x*, *y* and *z* axes) and translations (in *x*, *y* and *z*) that maximised the correlation between the image intensities of the volume in question and of the template (rigid-body registration). Following realignment, data were then smoothed using a Gaussian filter (full-width at half-maximum (FWHM) 7.2 mm) to improve the signal-to-noise ratio of the images (Bullmore, Brammer, et al., 1999). Following motion correction, global detrending, spin-excitation history correction and smoothing, time series analysis for each subject was conducted based on a previously published wavelet-based resampling method for fMRI data ((Bullmore et al., 2001; Bullmore, Suckling, et al., 1999). At the individual-subject level, a standard general linear modelling approach was used to obtain estimates of the response size (beta) to each of the task conditions against an implicit baseline. We first convolved the main experimental conditions with 2 Poisson model functions (peaking at 4 and 8s). We then calculated the weighted sum of these 2 convolutions that gave the best fit (least-squares) to the time series at each voxel. A

goodness-of-fit statistic (SSQ ratio) was then computed at each voxel consisting of the ration of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by that of the squares due to the residuals (original time series minus model time series). The appropriate null distribution for assessing significance of any given SSQ ratio was established using a wavelet-based data re-sampling method (Bullmore et al., 2001) and applying the model-fitting process to the resampled data. This process was repeated 20 times at each voxel and the data combined over all voxels, resulting in 20 null parametric maps of SSQ rations for each subject, which were combined to give the overall null distribution of SSQ ratio. This same permutation strategy was applied at each voxel to preserve spatial correlation structure in the data. Individual SSQ ratio maps were then affine transformed into standard space, by first mapping the fMRI data onto a high-resolution inversion recovery image of the same subject, and then by normalising onto a Talairach template.

A group-level activation map was produced for each group for each experimental condition (2s, 5s, 8s delays compared to sensory-motor control condition) by calculating the median observed SSQ ratios at each voxel in standard space across all subjects and testing them against the null distribution of median SSQ ratios computed from the identically transformed wavelet-resampled data (Brammer et al., 1997; Bullmore et al., 2001). ANOVAs were conducted using randomization-based tests for voxel- or cluster-wise differences (Bullmore et al., 1999). Only correct trials were included in the analysis. Premature responses were also modelled at the individual subject level as an event of non-interest, and ignored in subsequent group-level analyses. The voxel-level threshold was first set to $P < 0.05$ to give maximum sensitivity and to avoid Type II errors (Bullmore et al., 1999). Next, a cluster-level threshold was computed for the resulting 3D voxel clusters in such a way as to produce less than one false positive 3D cluster per map. The necessary combination of voxel and cluster level

thresholds was not assumed from theory but rather was determined by direct permutation for each dataset, giving excellent type-I and type-II error control (Bullmore et al., 1999). Cluster mass rather than a cluster extent threshold was used to minimize discrimination against possible small, strongly responding foci of activation (Bullmore et al., 1999). For the between-group comparisons, a 3 × 3 ANOVA (three time delays, three groups) was conducted testing for group, delay and group by delay interaction effects. For group and group by delay interaction, less than one false positive cluster per map was expected at $p<.05$ for voxel and $p<.02$ for cluster comparisons.

Additional regions of interest (ROI) analyses were performed according to *a priori* hypotheses. A single ROI search space was based on regions expected to differ between groups. This included the DMN regions A/VMPFC (Talairach coordinates: 0,50,-4; 18mm sphere)(Stern *et al.* 2012), and precuneus (extracted from the Talaraich atlas using XBAM), the CEN and VAN regions IFG (BA 44/45/47) and DLPFC (BA 8/9/46), and the SN regions the anterior insula (Talaraich coordinates: +/-35,14,5; 18mm sphere)(Stern *et al.* 2012) and mACC (Talaraich coordinates: 0,10,47; 18 mm sphere) (Stern *et al.* 2012). Within this search space, less than one false positive cluster per map was expected at $p<.05$ for voxel and $p<.05$ for cluster comparisons for group main effect and group by delay analyses.

Statistical measures of BOLD response (SSQ) for each participant were extracted in each of the significant clusters and post-hoc least significance difference t-tests (correcting for multiple comparisons) were conducted to identify between-group differences.

Statistical BOLD response from regions that showed a significant group by delay effect were extracted, and correlated with task performance and symptom scores within each group. Further exploratory examinations within each group for significant negative correlations

between activation from task-positive CEN, SN and VAN regions and activation from regions showing a significant group by delay effect were performed.

## 6.3. Results

### 6.3.1. Participant characteristics

There were no significant group differences in age, but IQ was significantly lower in ADHD (Table 6.1.). This was to be expected as ADHD is associated with lower IQ (Bridgett & Walker, 2006). However, IQ was not covaried in the first instance as covarying for differences between groups that were not randomly selected violates ANCOVA assumptions (Miller & Chapman, 2001). Nonetheless, supplementary analyses were performed covarying for IQ to rule out that IQ was a confounding factor (see below).

**Table 6.1. Participant characteristics.**

| | **Controls** | **ADHD** | **OCD** | **Sig.** | |
|---|---|---|---|---|---|
| N | 20 | 20 | 20 | - | |
| Age | 15.4 (1.43) | 15 (1.28) | 15.76 (1.43) | F(2,57)=1.46 , p=.24 | |
| IQ | 117.75 (12.10) | 101.7 (14.61) | 117.7 (13.36) | F(2,57)=9.5, p<.001 | C,OCD>ADHD |
| SDQ hyperactivity/inattention | 2 (1.71) | 8.16 (1.38) | 4.4 (3.03) | F(2,54)=37.78, p<.001 | ADHD>OCD>C |
| CY-BOCS | … | … | 22.32 (5.97) | | |
| Conner's T | … | 81.2 (9.95) | … | | |

*Abbreviations.* ADHD, attention-deficit/hyperactivity disorder; CYBOCS, Children's Yale-Brown Obsessive Compulsive Scale; IQ, intelligence quotient; OCD, obsessive/compulsive disorder; SDQ, strengths and difficulties questionnaire.

### 6.3.2. Performance data

There were no significant main effects of delay or significant group by delay interactions on reaction time, reaction time variability, premature responses or omission errors (p>.1). There

was a main effect of group for reaction time ($F(2,57)=4.74$, $p<.001$), driven by ADHD boys who showed slower reaction times relative to both controls ($p<.006$) and patients with OCD ($p<.029$), for reaction time variability ($F(2,57)=10.58$, $p<.001$), which was increased in ADHD patients relative to controls and OCD patients ($p<.001$) but not for omissions ($F(2,57)=.871$, $p=.424$) (Figures 6.2. & 6.3.). Results remained unchanged after controlling for IQ.

**Table 6.2. Performance measures for the sustained attention task for each delay for boys with ADHD, OCD and healthy controls.**

| Performance measure | Delay | Controls mean (SD) | ADHD mean (SD) | OCD mean (SD) |
|---|---|---|---|---|
| RT | 2s | 380.89(38.07) | 433.52(43.66) | 390.72(44.8) |
| | 5s | 377.52(42.68) | 414.26(56.45) | 386.29(48.95) |
| | 8s | 384.23(46.61) | 416.62(61.88) | 387.33(46.25) |
| RT variability | 2s | 66.51(28.37) | 98.39(34.13) | 68.19(23.39) |
| | 5s | 54.56(24.69) | 90.89(29.62) | 73.56(37.78) |
| | 8s | 63.99(23.48) | 99.99(42.77) | 63.32(32.4) |
| Omissions | 2s | 0.15(0.67) | .2(0.41) | 0(0) |
| | 5s | 0.2(0.89) | .15(0.49) | 0(0) |
| | 8s | 0.3(1.13) | .15(0.37) | 0(0) |

*Abbreviations:* ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive/compulsive disorder; RT = Mean Reaction Time (in ms).

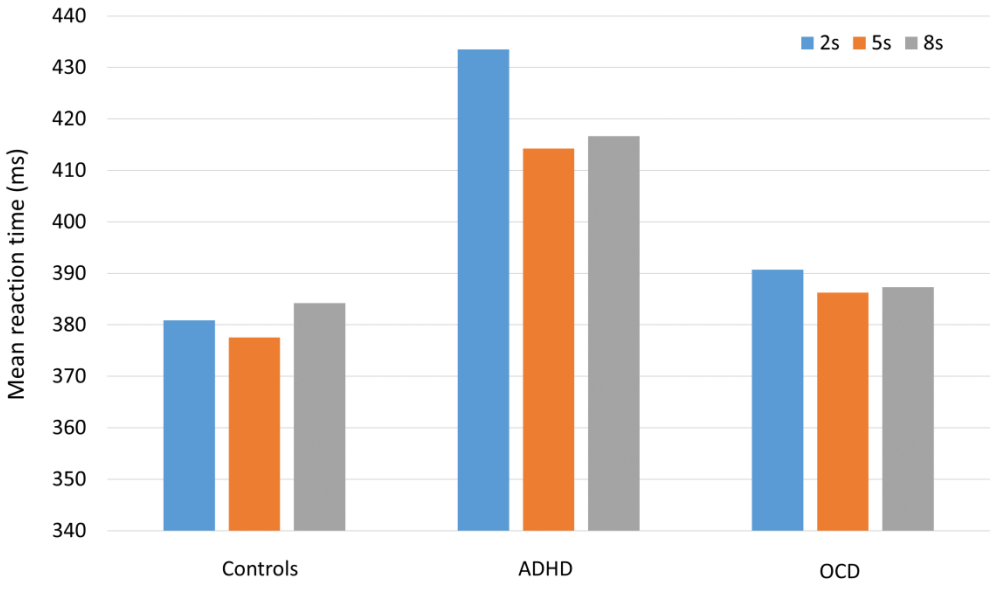



**Figure 6.2. Shows mean reaction times for each group for each delay length.**

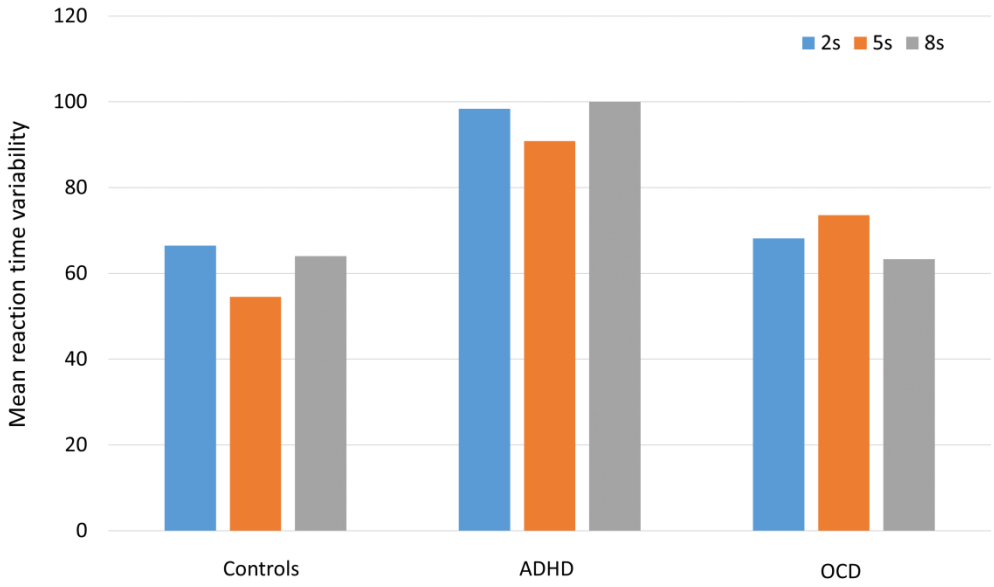



**Figure 6.3. Shows mean reaction time variability for each group for each delay length.**

### 6.3.3. Motion

There were no significant group differences in mean Euclidian displacement of x, y, z movement parameters ($F(2, 57)=.04$, $p=.96$).

### 6.3.4. Delay effect

When pooled, all participants showed a main effect of delay in bilateral DLPFC, IFG, AI, cingulate, temporal lobe, parietal lobe, cerebellum, basal ganglia, thalamus and hippocampal gyri (Figure 6.4.).

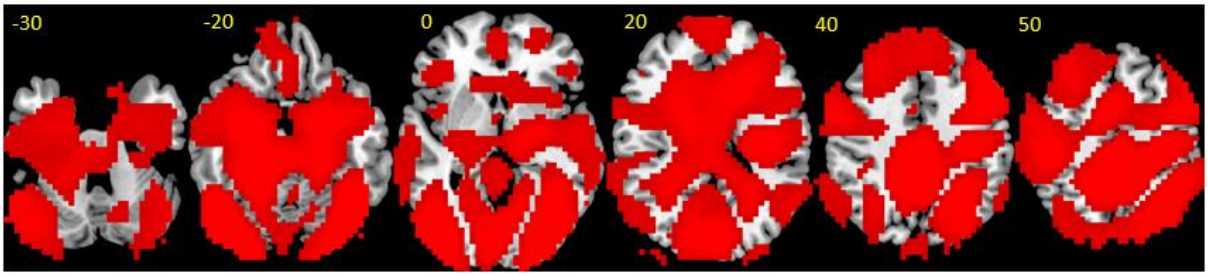



Figure 6.4. Horizontal slices showing split plot ANOVA effects of delay on brain activation for all subjects. The right side corresponds to the right side of the image.

### 6.3.5. Group effect

Whole-brain ANOVA split-plot analysis showed a significant main effect of group in bilateral cerebellum, lingual gyrus, cuneus (Table 6.3, Figure 6.5.). Post-hoc analyses showed that ADHD patients showed disorder-specific left cerebellum (anterior lobe, culmen) underactivation relative to controls and OCD patients. OCD patients showed disorder-specific increased activation in bilateral cerebellum (posterior lobe, culmen, declive/vermis/anterior lobe, culmen), lingual gyrus, and cuneus relative to ADHD patients and controls.

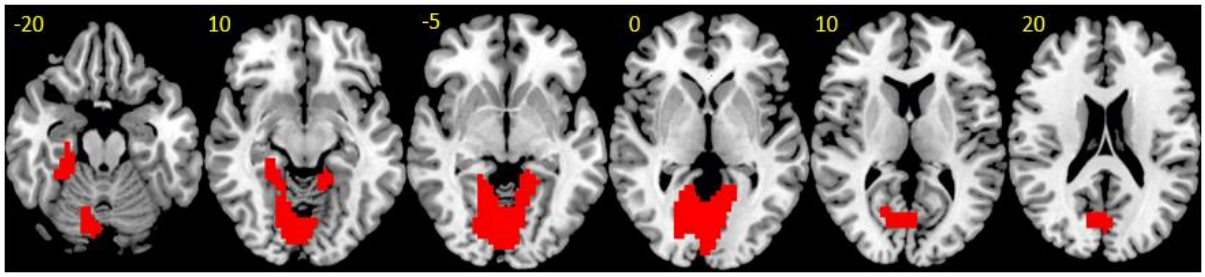



**Figure 6.5. Horizontal slices showing split plot ANOVA effects of group on brain activation for all subjects. The right side corresponds to the right side of the image.**

| Brain regions of activation | BA | TAL COORD | Voxels | Cluster p-value |
|---|---|---|---|---|
| **C,OCD >ADHD** | | | | |
| L cerebellum (anterior lobe, culmen) | | -4,-30,-29 | 5 | .047 |
| **OCD>C,ADHD** | | | | |
| L cerebellum (anterior lobe, culmen) | | -22,-33,-24 | 41 | .006 |

| | | | |
|---|---|---|---|
| R cerebellum (posterior lobe , declive/vermis)/lingual gyrus/cuneus | 7,-74,-13 | 152 | <.001 |
| R cerebellum (anterior lobe, culmen) | 18,-44,-13 | 28 | .004 |
| L cerebellum (anterior lobe, culmen)/lingual gyrus/cuneus | -11,-56,-7 | 147 | <.001 |
| R cerebellum (anterior lobe, culmen) | 14,-52,-7 | 44 | .004 |

**Table 6.3. ANCOVA group effect on brain activation between ADHD, OCD and healthy boys.**

*Abbreviations:* ADHD, Attention-Deficit/Hyperactivity Disorder; BA, Brodmann area; C, controls; OCD, obsessive/compulsive disorder; TAL COORD, Talairach coordinates.

*Note: Local maxima that were farther apart than the upper bound of the likely Talairach mapping error (3 voxel radius:10 mm) were identified (Thirion et al. 2007). Voxels were then assigned to the nearest local maximum with a statistic value that exceeded that of the voxels. The probabilities for this contrast are given for sub-cluster maxima.*

### 6.3.6. Group by delay effects

Whole-brain ANOVA split-plot analysis group by delay interaction effects were significant in left insula/ventral IFG, left DLPFC/dorsal IFG, mACC, left caudate/putamen, bilateral cerebellum/occipital/parahippocampus/hippocampus, right precuneus and bilateral dACC (Table 6.4., Figures 6.6. & 6.7.). Follow-up t-tests revealed that decreased left insula/ventral IFG activation was shared in ADHD and OCD relative to controls, and due to progressively increased activation in his region in controls with increasing delays but progressively decreased activation with increasing delay in both patient groups. A region of right cerebellum (posterior lobe, inferior semilunar lobule) showed increasing activation with increasing delays in controls, but not in ADHD and OCD patients. Decreased recruitment of left DLPFC/dorsal IFG was driven by ADHD patients who showed progressively decreased activation with increasing delays relative to controls and OCD patients who showed progressively increased activation with increasing delay. Findings in mACC, left caudate/putamen and regions of right cerebellum (posterior lobe, uvula/declive/tonsil) were

driven by disorder-specific progressively decreasing activation with increasing delays in OCD patients relative to controls and patients with ADHD. Activation in bilateral cerebellum (posterior lobe, declive/vermis)/occipital lobe was progressively increased in OCD with increasing delay relative to controls and ADHD patients. Left cerebellum (anterior lobe, culmen)/parahippocampus/hippocampus was progressively increased in activation in OCD relative to ADHD, and part of right precuneus showed increasing activation with longer delays in OCD but progressively decreasing activation with longer delays in controls. Right and left dACC and right precuneus were increased in activation in ADHD relative to controls and patients with OCD, who showed progressive deactivation in these regions with increasing delay. Results remained in a sub-group analysis of 13 medication naïve patients with ADHD, 16 medication naïve patients with OCD, and 20 healthy controls.

The ROI analysis showed an additional cluster in the A/VMPFC (Talaraich coordinates, 67,-2,41; BA 10/11, 28 voxels, P<.05) which was disorder-specifically increased in activation with increasing delay in OCD relative to ADHD and control boys. See Figure 6.8.

All group by delay effects results remained after covarying for IQ.

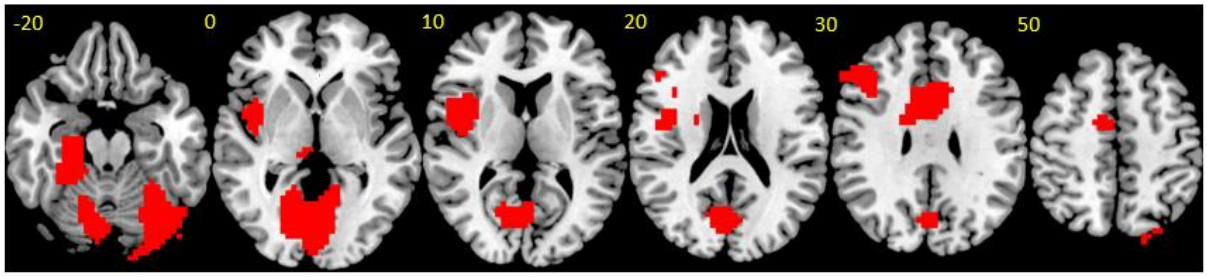



**Figure 6.6. Horizontal slices showing whole-brain split plot analysis of variance (ANOVA) effects of group by delay interactions on brain activation.** The right side corresponds to the right side of the image.

(a)

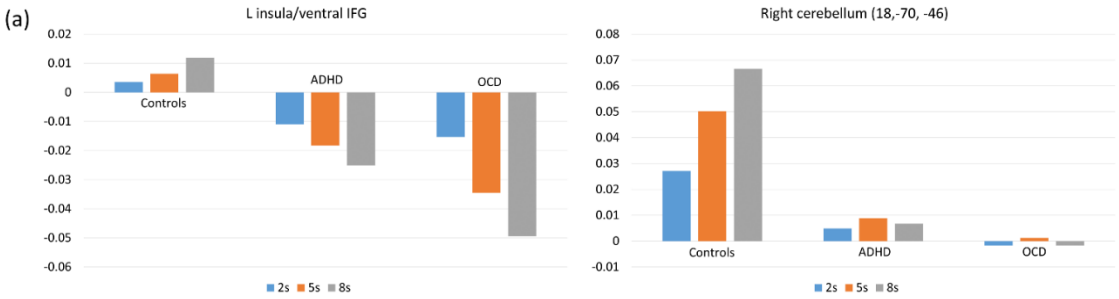

L insula/ventral IFG
0.02
0.01
0
-0.01
-0.02
-0.03
-0.04
-0.05
-0.06
Controls
ADHD
OCD
2s 5s 8s
Right cerebellum (18,-70, -46)
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
-0.01
Controls
ADHD
OCD
2s 5s 8s

**Table 6.4. ANCOVA group by delay interaction effect on brain activation between ADHD, OCD**


**Figure 6.7. Statistical measures of BOLD response for each of the three groups for each of the brain regions that showed a significant group by delay effect.** (a) Shows findings shared in ADHD and OCD, (b) shows findings disorder-specific in ADHD, and (c) shows findings disorder-specific in OCD.

**and healthy boys**

| Brain regions of activation | BA | Peak Talairach Coordinates | Voxels | Cluster p-value |
|---|---|---|---|---|
| **C > ADHD,OCD** | | | | |
| L insula/IFG | 13/44/45 | -40,4,-2 | 114 | .001 |
| R cerebellum (posterior lobe, inferior semilunar lobule) | | 18,-70,-46 | 36 | .005 |
| **OCD < C, ADHD** | | | | |
| mACC | 24/23/6 | -4,0,31 | 87 | .001 |
| R caudate/putamen | | -18,0,15 | 19 | .05 |
| R cerebellum (posterior lobe, uvula) | | 33,-63,-24 | 91 | .001 |
| R cerebellum (posterior lobe, declive) | | 36,-81-18 | 93 | .001 |
| R cerebellum (posterior Lobe, cerebellar tonsil) | | 33,-19,-46 | 31 | .005 |
| R cerebellum (posterior Lobe, cerebellar tonsil) | | 36,-44,-35 | 70 | .001 |
| **OCD > ADHD,C** | | | | |
| L & R cerebellum (posterior lobe, declive/vermis), lingual gyrus/cuneus | 17/18 | 7,-74,-13 | 200 | .001 |
| L cerebellum (anterior lobe, culmen) | | -22,-33,-24 | 60 | .005 |
| L cerebellum (anterior lobe, culmen) | | -11,-52,-13 | 167 | .001 |
| **ADHD < C, OCD** | | | | |
| L DLPFC/IFG | 9/46/44/45 | -40,30,26 | 144 | .001 |
| **OCD>C** | | | | |
| R precuneus | 7 | 11,-59,31 | 55 | .05 |
| **ADHD < OCD** | | | | |
| L cerebellum (anterior lobe, culmen), parahippocampus/hippocampus | | -11,-22,-18 | 75 | .05 |
| **ADHD > C,OCD** | | | | |
| R precuneus/superior occipital | 7/19 | 33,-74,37 | 55 | .001 |

| | | | | |
|---|---|---|---|---|
| R dACC | 33/24 | 7,19,20 | 59 | .002 |
| L dACC | 33/24 | -4,11,20 | 39 | .05 |

*Abbreviations:* ADHD, Attention-Deficit/Hyperactivity Disorder; BA, Brodmann area; C, controls; dACC, dorsal anterior cingulate; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; mACC, middle anterior cingulate; OCD, obsessive/compulsive disorder.

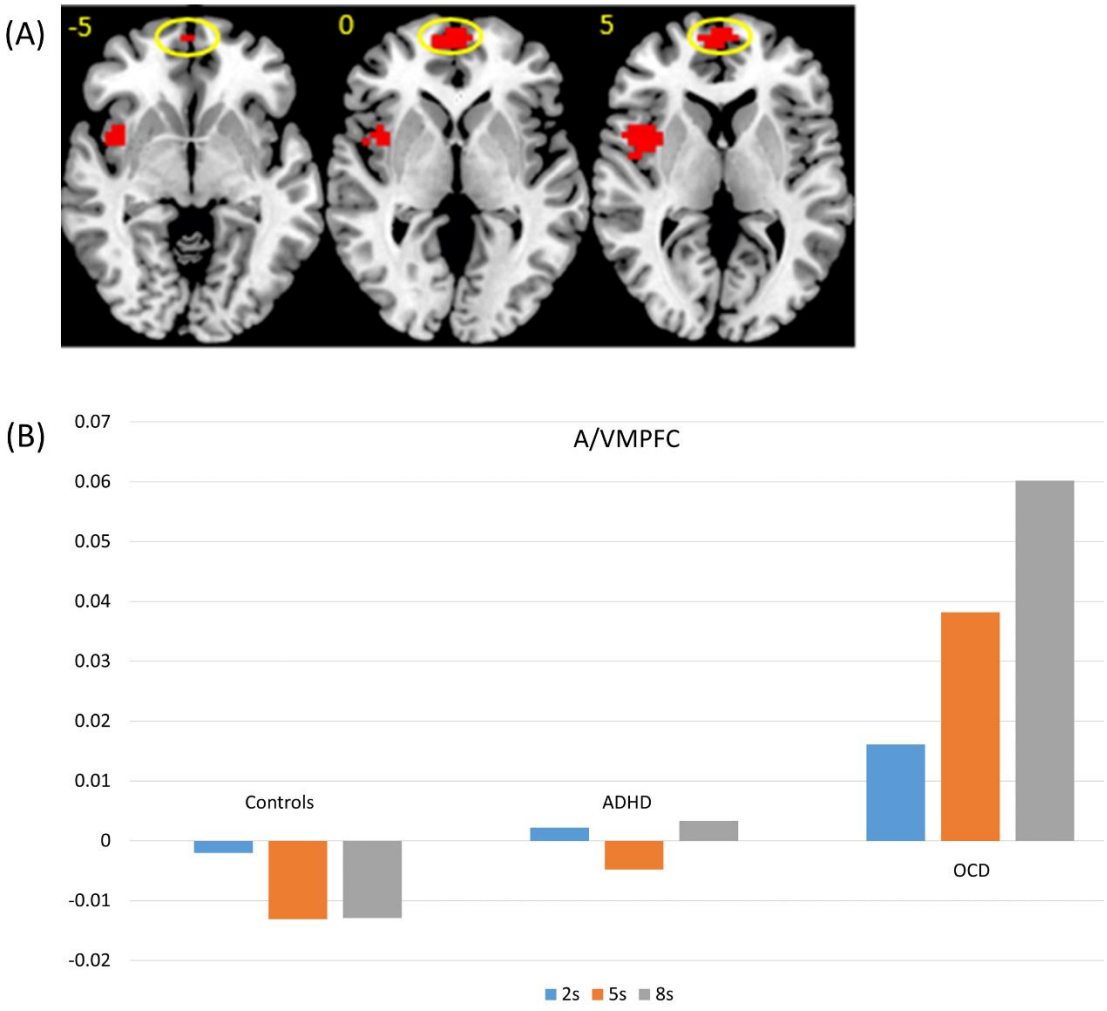



**Figure 6.8. Increased A/VMPFC activation within ROI search space during sustained attention in patients with OCD.** (A) Horizontal slices showing split plot analysis of variance (ANOVA) effects of group by delay interactions within ROI search space. Circled is the A/VMPFC cluster. The right side corresponds to the right side of the image. (B) Statistical measures of BOLD response are shown for each of the three groups for the A/VMPFC cluster that showed a significant group by delay effect within the ROI search space.

### 6.3.7. Exploratory brain-behaviour and brain-performance correlations

Within controls, activation in right cerebellum (posterior lobe, cerebellar tonsil) positively correlated with reaction time (r(20)=.789, p<.001) and reaction time variability (r(20)=.620, p=.004). Within the ADHD group, activation in left insula/ventral IFG correlated positively with reaction time (r(20)=.455, p=.044) and reaction time variability (r(20)=.457, p=.043). In OCD patients, a significant positive correlation was found between reaction time and activation in right cerebellum (posterior lobe, inferior semilunar lobule) (*r*(20)=.459, p=.042). However, these findings did not survive correction for multiple comparison using the Benjamini and Hochberg method (Benjamini & Hochberg, 1995).

There were no significant correlations between CY-BOCS scores and brain activation in the group difference clusters in the OCD patients. There was a significant negative correlation between scores on the SDQ inattention/hyperactivity scale and right cerebellum (posterior lobe, cerebellar tonsil) activation in ADHD patients (r(19)=-.528, p=.02), although this did not survive correction for multiple comparisons.

To test whether regions of the CEN/VAN/SN were anti-correlated with regions of the DMN, we conducted correlations between left DLPFC/dorsal IFG, left insula/IFG, and mACC, and A/VMPFC, dACC and right precuneus within each group. Within controls, activation in DLPFC/dorsal IFG had a significant negative correlation with activity in A/VMPFC (r(18)=-.507, p=.023) and in left dACC (r(18)-.467, p=.038), and mACC activation had a significant negative correlation with A/VMPFC (r(18)=-.482, p=.032). Greater activation in left insula/ventral IFG was associated with decreased activation in right precuneus in ADHD (r(18)=-.615, p=.004) and OCD (r(18)=-547,p=.013). In ADHD patients alone, activation in left insula/ventral IFG and mACC had significant positive correlations with left dACC (left insula/IFG; r(18)=.573, p<.001, mACC; r(18)=.489, p=.029), while left insula/ventral IFG activation had a significant positive correlation with right dACC activation (r(18)=.550,

p=.012). In OCD patients, activation in the mACC had a significant negative correlation with activation in right precuneus (r(18)=-.455, p=.044) and positive correlations with bilateral dACC (left; r(18)=.684, p<.001; r(18)=.678, p=.001). Only the correlations between mACC and dACC in OCD survived correction for multiple comparisons.

### 6.4. Discussion

This study investigated shared and disorder-specific neurofunctional abnormalities in patients with ADHD and with OCD during a sustained/focused attention task. Patients with ADHD and OCD showed shared underactivation in right cerebellum and left insula extending into a relatively ventral portion of IFG. However, they also showed disorder-specific brain dysfunction in frontal regions of attention networks as well as in frontal regions of the DMN. Patients with ADHD showed disorder-specific progressively decreased activation with increasing delay relative to healthy control and OCD boys in key task-relevant CEN regions of left DLPFC extending into a relatively more dorsal portion of IFG while OCD patients showed progressively decreased activation with increasing delay in SN region the mACC (posterior portion of ACC). In dACC, controls and OCD patients showed progressively decreased activation with increasing delays while ADHD patients did not show this pattern. On the other hand, in A/VMPFC, OCD patients showed progressively increased activation with progressive delays, while controls showed progressive deactivation with increasing delays in this region.

Decreased recruitment of task-positive CEN and VAN DLPFC/dorsal IFG regions in ADHD is in line with previous studies of sustained attention in the disorder (Christakou, Murphy, et al., 2013; Cubillo et al., 2012; Rubia, Halari, Cubillo, et al., 2009a; Rubia, Smith, et al., 2009), as well as with evidence that decreased IFG GMV predicts poor sustained attention performance in ADHD (Pironti et al., 2014). Previous research has shown disorder-specificity

in ADHD in the IFG during attention tasks relative to conduct disorder (Rubia, Halari, Smith, et al., 2009; Rubia, Smith, et al., 2009), and during inhibitory control tasks relative to conduct disorder (Rubia, Halari, et al., 2010), bipolar disorder (Passarotti et al., 2010a, 2010b) and OCD (Chapter 5) (Rubia, Cubillo, et al., 2010; Rubia, Cubillo, et al., 2011), while underactivation of left DLPFC during sustained attention has previously been found relative to patients with autism (Christakou, Murphy, et al., 2013). The current results extend these previous findings of disorder-specific underactivation in ADHD patients in left lateral prefrontal regions by demonstrating disorder-specificity relative to OCD in left DLPFC/dorsal IFG during sustained attention, and provide further evidence that IFG underactivation is a biomarker most closely associated with ADHD than to other childhood disorders (Rubia, Alegria, & Brinson, 2014). Findings of shared underactivation in ventral IFG, but disorder-specific underactivation in dorsal IFG in ADHD, are consistent with evidence that sub-regions of the IFG have distinct patterns of structural and functional connectivity, with the dorsal portions of the IFG being more closely integrated with CEN regions, including adjacent DLPFC (Barredo, Verstynen, & Badre, 2016). Underactivation in left DLPFC/dorsal IFG may be related to a maturational delay, as these regions have been found to be delayed in structure and function in ADHD patients (Rubia, Alegria, & Brinson, 2014; Shaw et al., 2012; Sripada, Kessler, & Angstadt, 2014)

Patients with OCD showed disorder-specific underactivation relative to ADHD in mACC, extending previous evidence for decreased activation during cognitive tasks and GMV in this region compared to healthy controls (Carmona et al., 2007; Kang et al., 2013; Page et al., 2009; Rubia, Cubillo, et al., 2010; Woolley et al., 2008) by showing disorder-specificity relative to ADHD. Disorder-specific underactivation in this region relative to ADHD is in line with the meta-analysis, which found medial prefrontal underactivation and decreased GMV to be disorder-specific in OCD relative to ADHD (Chapter 5). Findings of disorder-

specific mACC underactivation in OCD and DLPFC/dorsal IFG underactivation in ADHD therefore support accounts proposing that primary prefrontal deficits in ADHD are in dorsal and especially inferior lateral prefrontal cortex, while primary prefrontal deficits in OCD are within medial prefrontal cortex (Chapter 5) (Rubia, Alegria, & Brinson, 2014).

Both ADHD and OCD boys shared underactivation in left insula extending into ventral IFG. The insula and ventral IFG are key task-positive regions and the central hubs of the SN and VAN involved in switching from the DMN to CEN on the basis of stimuli indicating the need for external attention (Cai et al., 2014; Menon, 2011; Menon & Uddin, 2010; Seeley et al., 2007), or based on a need to suppress mind-wandering and remain vigilant for upcoming stimuli (Hasenkamp, Wilson-Mendenhall, Duncan, & Barsalou, 2012; Langner & Eickhoff, 2013). In ADHD, insufficient activation of the insula and ventral IFG has been reported previously during sustained attention (Cubillo et al., 2012; Rubia, Halari, Cubillo, et al., 2009a; Rubia, Smith, et al., 2009), attention allocation (Rubia, Halari, Smith, et al., 2009; Rubia, Smith, Brammer, et al., 2007), and inhibitory control tasks (Cortese et al., 2012; Hart et al., 2013; Lei, Du, et al., 2015; Rubia, Cubillo, et al., 2010; Rubia, Halari, Smith, et al., 2009). It is proposed to underlie decreased task-related salience and resultant heightened distractibility (Chapter 5). In OCD, heightened insula related activation is reported to errors (Stern et al., 2011) during affective processing (Berlin et al., 2015), and during symptom provocation (Brennan et al., 2015; Rotge et al., 2008), although there is some evidence for decreased activation during cognitive tasks (Gu et al., 2008; Huyser et al., 2011; Woolley et al., 2008). Findings are also in line with resting-state fMRI evidence showing decreased negative connectivity between insula and DMN including A/VMPFC (Stern et al., 2012) and decreased insula, but increased A/VMPFC activity at rest in OCD (Zhu et al., 2016).

Interestingly, we recently showed in our comparative meta-analysis that underactivation of the insula/ventral IFG during inhibitory control was disorder-specific to patients with ADHD

relative to patients with OCD (Chapter 5), while a posterior insula/putamen cluster was increased in activation in OCD, whereas in the current study reduced insula/ventral IFG activation was shared. Discrepant findings are likely due to differences in task conditions. Insula/ventral IFG deficits in OCD may be dependent on conditions which invite greater DMN, such as long delays (Christoff et al., 2009; Hasenkamp et al., 2012), an interpretation which is supported by findings of decreases in insula activation and increases in DMN activation with increasing delays in OCD.

Both groups showed increased activation within the DMN, supporting accounts wherein deficient switching from DMN to task-positive networks underlies problems with sustained attention in ADHD and OCD (Christakou, Murphy, et al., 2013; Metin et al., 2015; Sonuga-Barke & Castellanos, 2007). Findings are consistent with a role for attention lapses caused by poor control over DMN mediated task-unrelated thoughts (Raichle, 2015), which have been shown to occur more often in both patient groups (Mowlem et al., 2016; Seli et al., 2016; Seli et al., 2015), and to be associated with poor sustained attention performance (Thomson et al., 2015). In ADHD, disorder-specific reduced deactivation was seen in dACC. In contrast, in OCD, disorder-specific alterations were found in A/VMPFC, which showed disorder-specific increases in activation with increasing delays. Both patient groups showed increased activation relative to controls in portions of the precuneus. Patients with ADHD have previously shown reduced deactivation of the ACC during cognitive tasks (Fassbender et al., 2009; Liddle et al., 2011; Metin et al., 2015; Peterson et al., 2009). Shared hyperactivity in the precuneus in both disorders is in line with previous research in ADHD (Christakou, Murphy, et al., 2013; Cubillo et al., 2012; Durston et al., 2003; Liddle et al., 2011; Rubia, Smith, et al., 2009) and OCD (Kang et al., 2013; Page et al., 2009; Roth et al., 2007). The A/VMPFC is a key region of DMN and a commonly implicated region in OCD. It has shown increased activity at rest (Menzies et al., 2008; Zhu et al., 2016), during symptom

provocation (Brennan et al., 2015; Rotge et al., 2008), and during cognitive tasks (Agam et al., 2014; Brennan et al., 2015; Page et al., 2009; Stern et al., 2011; Stern et al., 2013) in OCD patients. Furthermore, in a meta-analytic comparison of VBM studies, disorder-specific increased GMV was found in paediatric OCD relative to paediatric ADHD (Chapter 5). Given its role in internally generated thought and its hyperactivation in OCD, it could be hypothesised that A/VMPFC is a plausible correlate of intrusive obsessive thoughts (Stern et al., 2012; Stern et al., 2013), which is poorly controlled by task-positive networks during sustained attention. In sum, increased activation in the posterior DMN region in precuneus during sustained attention may be a shared feature of both disorders, although perturbations in separate anterior DMN regions appear to be largely disorder-specific.

Only patients with ADHD showed a performance difference relative to controls, with slower response times and greater reaction time variability, consistent with previous research (Christakou, Murphy, et al., 2013; Huang-Pollock et al., 2012). Previous meta-analyses of sustained attention tasks in OCD adults have reported significant behavioural deficits relative to controls (Abramovitch et al., 2013; Benzina et al., 2016; Shin et al., 2008). However, the current negative result is in line with previous studies which have examined sustained attention in OCD youths (Lucke et al., 2015; Shin, Lee, et al., 2014). Neuropsychological impairments are more prominent in adult than paediatric OCD (Abramovitch et al., 2013; Abramovitch, Abramowitz, et al., 2015), which may reflect altered developmental trajectories and a failure to maintain age normative cognitive performance with increasing demands (Abramovitch, Abramowitz, et al., 2015). Consistent with previous neuroimaging studies of OCD (Rubia, Cubillo, et al., 2010; Rubia, Cubillo, et al., 2011; Woolley et al., 2008), neural activation was found to be a more sensitive measure of between group differences, and is indicative of alterations in brain networks responsible for sustained attention in paediatric OCD. The study used a simplified attention task with low cognitive demands, which was

designed to minimize errors thereby allowing for enough correct trials for use in fMRI analysis. Deficits in brain activation may be a more sensitive measure of abnormalities in cognitive brain networks than behavioural performance in these simplified tasks, as normal performance can be maintained when demands are low despite neural dysfunction (Page et al., 2009; Woolley et al., 2008).

Patients with OCD showed increased activation relative to controls and patients with ADHD in medial cerebellum, but showed decreased activation in lateral cerebellum, whereas ADHD patients showed disorder-specific decreased activation in a distinct portion of medial cerebellum. As in previous studies of attention tasks in ADHD, cerebellar underactivation correlated with ADHD symptoms (Cubillo et al., 2011; Rubia, Smith, Brammer, et al., 2007). Patient groups shared underactivation in a portion of inferior cerebellum relative to controls. The cerebellum forms part of CEN, SN, DMN and sensorimotor networks, although its role in each of these is poorly understood, making the current findings difficult to interpret (Habas et al., 2009). Patients with OCD and with ADHD have shown both increased and decreased cerebellar activation in previous studies using cognitive tasks (Kang et al., 2013; Page et al., 2009; Rubia, Halari, Cubillo, et al., 2009b; Rubia, Smith, et al., 2009; Woolley et al., 2008), and these findings, along with the ones presented here, are likely a result of as yet poorly defined cerebellar functional heterogeneity.

A limitation of the study is that the ADHD group had lower IQ relative to the other groups. However, lower IQ is typical for this population and the results remained when we covaried for IQ. Second, 35% of patients with ADHD were receiving psychostimulant medication, which may have mitigated group differences (Hart et al., 2013; Rubia, Alegria, Cubillo, et al., 2014) although patients received a 48-hour washout period, which is more than 10 times the half-life of the drug. Failures of DMN activation are interpreted based on neuroanatomical overlap with previous work (Metin et al., 2015; Raichle, 2015; Stern et al., 2012), as well as

findings in the current study that these brain regions showed deactivation during task performance and/or significant negative correlations with task-positive regions in controls. However, alternative explanations, for instance that regions of increased activation served as compensatory strategies in patient groups, are also plausible.

In summary, sustained attention performance in patients with ADHD and OCD was associated with largely disorder-specific patterns of activation abnormalities in task-positive attention control and DMN regions. Consistent with previous research, deficits in lateral prefrontal (DLPFC/IFG) CEN regions important for goal-directed attention and behaviour were disorder-specific to ADHD relative to controls and OCD, while deficits in mACC were disorder-specific to OCD. In the DMN, both groups showed overactivation in different regions of the precuneus, while dACC overactivation was disorder-specific to ADHD and A/VMPFC overactivation was disorder-specific to OCD with increasing sustained attention load. Shared underactivation in SN and VAN suggests shared deficits in switching attention from interoceptive to exteroceptive focus. Shared and disorder-specific patterns of altered activation suggest that, rather than representing a shared transdiagnostic mechanism, deficits in sustained attention in ADHD and OCD represent phenocopies, with both shared and disorder-specific underlying neural correlates. The results are consistent with results originating from the field of behaviour genetics, according to which ADHD and OCD symptom liability appears to be determined to a greater extent by disorder-specific genetic influences, underlining that these disorders are not alternative phenotypic expressions of the same underlying genetic liability (Pinto et al., 2016).

## Chapter 7. Shared and disorder-exclusive neural dysfunction during temporal discounting in paediatric ADHD and OCD.

### 7.1. Introduction

ADHD affects 3-8% of children worldwide and 4% of adults (Biederman et al., 2012), and is defined by age-inappropriate problems with inattention, impulsivity and hyperactivity (American Psychiatric Association, 2013).

OCD has a lifetime risk of 2-3% (Ruscio et al., 2010). The key symptoms are obsessions, i.e. recurrent and intrusive thoughts (e.g., on themes of contamination, checking, orderliness and symmetry), and compulsions, i.e. repetitive, ego-dystonic and time-consuming behavioural and mental rituals (e.g., repetitive washing or checking) (American Psychiatric Association, 2013).

Impulsiveness is a multifaceted construct and typified by a premature, poorly controlled, poor foresighted, delay averse response pattern where the consequences of acts are not considered (Fineberg et al., 2014; Rubia, 2002; Rubia, Halari, Christakou, et al., 2009). One of the key aspects of impulsiveness is choice impulsiveness, the inability to adequately pursue long-term goals due to a tendency to act in accordance with competing, immediate impulses or motivational states, while not considering the future consequences of behaviour due to insufficient temporal foresight (Fineberg et al., 2014; Hamilton et al., 2015; Rubia, Halari, Christakou, et al., 2009). Impulsivity is a core feature of ADHD, which is particularly prevalent during childhood and adolescence (American Psychiatric Association, 2013). OCD is also associated with impulsivity, which is furthermore associated with poorer treatment outcomes (Kashyap et al., 2012). Compulsivity and impulsivity are traditionally situated at opposing ends of a compulsivity-impulsivity spectrum, with OCD considered the archetypal disorder of compulsivity (Fineberg et al., 2014; Robbins et al., 2012). However, recent research suggests that compulsivity and impulsivity are in fact orthogonal constructs that may

co-exist in OCD (Fineberg et al., 2014; Kashyap et al., 2012; Sohn et al., 2014). In particular, impulsivity is hypothesised to be manifested as a tendency to perform behavioural rituals in order to bring about an initially rewarding outcome (i.e., relieve anxiety) despite negative long-term consequences (Fontenelle et al., 2015; Grassi et al., 2015), but repeated rituals become habit-like compulsions (Gillan & Robbins, 2014).

To date, most neuroimaging studies of impulsivity in ADHD and OCD have focused on tasks involving inhibitory control or motor impulsivity, i.e. the poor ability to inhibit inappropriate prepotent responses during motor response inhibition paradigms such as go/no-go and stop tasks. Recent fMRI studies and a large meta-analysis have provided evidence for disorder-specific fronto-insula-striatal activation abnormalities in the two disorders, with lateral inferior prefrontal and striatal underactivation being disorder-specific to ADHD (Chapter 5) (Rubia, Cubillo, et al., 2010; Rubia, Cubillo, et al., 2011), and medial frontal dysfunction and striatal hyperactivation being disorder-specific to OCD (Chapter 5). However, impulsivity is a multifaceted construct (Fineberg et al., 2014), and much less research has examined the neural basis of other impulsivity domains such as choice impulsivity, which is also a feature of ADHD and OCD (Jackson & MacKillop, 2016; Noreika et al., 2013; Patros et al., 2016; Sohn et al., 2014).

Choice impulsivity is often measured in TD tasks (Christakou et al., 2011; Fineberg et al., 2014; Hamilton et al., 2015), during which participants are provided with a series of choices between small immediate rewards and larger rewards available after a hypothetical temporal delay, typically ranging from weeks to years. TD refers to the fact that the subjective values of rewards available after a temporal delay decrease as a function of the length of the temporal delay (Christakou et al., 2011; Hamilton et al., 2015). In studies incorporating adjusting-amount procedures (Carlisi et al., 2016; Christakou et al., 2011; Richards et al., 1997), adjustments of the immediate reward are performed according to the individual

participant's previous choices using an online algorithm, such that the range of options are narrowed around the point where the subjective value of the immediate reward is equal to that of fixed delayed reward (the indifference point) (Carlisi et al., 2016; Christakou et al., 2011; Richards et al., 1997). Indifference points across different delay lengths are used to produce a discounting curve, which is typically hyperbolic (i.e., as delay periods become longer, the rate at which reward values are declined decreases more drastically) (Peters & Buchel, 2011). The steepness of discounting curves varies widely between individuals, and steeper discounting indicates more impulsive choices (Hamilton et al., 2015; Peters & Buchel, 2011). The task measures several cognitive functions, such as the inhibition of the immediate thrill of the reward, the sensitivity of an individual to the varying real or hypothetical delay of time in units of reward (delay aversion), temporal foresight to understand the future gain of the delayed choice, as well as inter-temporal decision-making and reward evaluation with respect to its delay (Christakou et al., 2011; Hamilton et al., 2015; Noreika et al., 2013; Rubia, Halari, Christakou, et al., 2009).

Performance during TD tasks relies on two main brain networks (Christakou et al., 2011; Hare, Hakimi, & Rangel, 2014; Peters & Buchel, 2011). The first of these involves the VS, vmOFC and PCC, i.e. paralimbic regions involved in processing rewards and motivation (Christakou et al., 2011; Peters & Buchel, 2011). The second network involves inferior, rostrolateral, and dorsolateral prefrontal cortex, anterior insula, dorsal striatum, parietal lobe and cerebellum, i.e. regions involved in EFs such as inhibitory control (Hart et al., 2013; Wesley & Bickel, 2014), working memory (Nee et al., 2013; Wesley & Bickel, 2014), planning (van den Heuvel et al., 2003), prospection (Burgess, Gonen-Yaacovi, & Volle, 2011), reappraisal (Delgado, Gillis, & Phelps, 2008; Giuliani, Mann, Tomiyama, & Berkman, 2014; Kober et al., 2010; Volkow et al., 2010), time estimation (Hart et al., 2012; Noreika et al., 2013; Rubia, Halari, Christakou, et al., 2009) and attentional control (Hart et al., 2013;

Rubia, Cubillo, et al., 2011), processes which are important for making farsighted delayed choices (Christakou et al., 2011; Rubia, Halari, Christakou, et al., 2009; Wesley & Bickel, 2014). ADHD patients have shown steeper discounting rates than controls in TD tasks and reduced activation in EF regions including IFG, insula and dorsal striatum during delayed choices (Carlisi et al., 2016; Rubia, Halari, Christakou, et al., 2009), as well as altered correlations between IFG, temporal lobe, anterior insula, SMA and cerebellum activation and TD discounting rates relative to controls (Chantiluke et al., 2014). In adult ADHD, reduced activation has been reported in DLPFC, striatal, parietal and cerebellar regions when choosing between immediate and delayed choices (Ortiz et al., 2015; Plichta et al., 2009).

Impulsive decision-making is also a feature of OCD (Cavedini et al., 2002; Kashyap et al., 2012; Sohn et al., 2014), including during TD (Sohn et al., 2014). No fMRI studies have tested the underlying neurofunctional mechanisms of TD in OCD. However, previous research has established the importance of vmOFC and striatal regions in OCD (Menzies et al., 2008; Radua & Mataix-Cols, 2009; Radua et al., 2010; Saxena & Rauch, 2000), which are reliably activated during symptom provocation (Rotge et al., 2008), dysfunctional during cognitive (Chapter 5) and reward tasks (Remijnse et al., 2009), and highly relevant to TD (Christakou et al., 2011; Peters & Buchel, 2011). Abnormalities have also been reported in key TD regions including DLPFC, IFG, insula, parietal lobes and cerebellum (Chapter 5).

Furthermore, it is not clear to what extent the underlying brain mechanisms of TD differ or are shared between disorders as no published studies have directly compared ADHD and OCD patients during TD using fMRI. Shared neural dysfunction would lend credence to the idea that impulsive decision-making in ADHD and OCD is a shared transdiagnostic mechanism, whereas disorder-differentiated patterns of functional abnormalities would suggest that shared decision-making impairments are similar phenocopies associated with distinct underlying mechanisms (Robbins et al., 2012).

The aim of this study was therefore to conduct the first direct comparison of the neurofunctional substrates of TD in ADHD and OCD patients using fMRI. We hypothesised shared underactivation in both disorders relative to controls in striatal, DLPFC and cerebellar regions previously implicated in ADHD (Carlisi et al., 2016; Hart et al., 2013) and OCD (Rubia, Cubillo, et al., 2010; Rubia, Cubillo, et al., 2011), as well as in TD (Hamilton et al., 2015; Peters & Buchel, 2011). We, however, hypothesised more prominent or disorder-specific abnormalities in OCD patients in vmOFC regions (Menzies et al., 2008), and larger or disorder-specific underactivation in IFG in ADHD patients relative to controls and OCD patients (Hart et al., 2012; Noreika et al., 2013; Rubia, Halari, Christakou, et al., 2009).

## 7.2. Methods

### 7.2.1. Participants

Sixty-six (26 ADHD, 20 OCD, 20 controls) right handed (Oldfield, 1971) male adolescents participated, aged between 12-18, and with an IQ>70 as measured by the WASI-R short form (Wechsler, 2008). ADHD boys were recruited from local CAMHS and met DSM-IV criteria for inattentive/hyperactive-impulsive combined subtype, as assessed using the standardized Maudsley diagnostic interview (Goldberg & Murray, 2006), and scored above clinical cut-off on the CPRS-R (Conners et al., 1998) and the inattention/hyperactivity scale of the parent SDQ (Goodman, 1997). Twelve boys were medication naïve. Fourteen were receiving psychostimulant medication and underwent a 48 hour washout period prior to scanning. OCD boys were recruited from a national specialist clinic for child and adolescent OCD and local CAMHS and had clinical diagnoses of OCD, assessed according to ICD-10 criteria and the CY-BOCS (Scahill et al., 1997). Sixteen boys were medication naïve, while four were being treated with SSRI medication. Control participants had no diagnoses of any psychiatric conditions, and were recruited using local advertising.

Ethical approval was obtained from the local Research Ethics Committee (05/Q0706/275), and the study was conducted in accordance with the Declaration of Helsinki. Study details were explained to both child and guardian. Written informed consent was obtained for all participants.

### 7.2.2. Temporal discounting fMRI task

In each trial of the TD task (Carlisi et al., 2016; Chantiluke et al., 2014; Christakou et al., 2011; Rubia, Halari, Christakou, et al., 2009) participants are presented with the choice of an amount of money (£100) available after a delay or a smaller amount of money available immediately (0-£100). Delay lengths are one week, one month and one year. For each participant, an algorithm is used to find values for the immediate option which are treated subjectively as equivalent to the larger delayed option for each delay length, thus ensuring each participant makes an equal number of immediate and delayed choices (Carlisi et al., 2016; Chantiluke et al., 2014; Christakou et al., 2011; Rubia, Halari, Christakou, et al., 2009). Immediate options are presented on the left side of the screen and are selected by pressing a button placed under the right index finger. Delayed options are presented on the right side of the screen and are selected with the right middle finger. Each trial lasts for 4s, separated by blank screen interval of at least 8s (depending on the participant's reaction time) which acts as an implicit baseline in the fMRI analysis (inter-trial-interval: 12s). Participants complete twenty trials for each delay length, and complete 60 trials overall (Figure 7.1.). All participants completed an initial practice session of the task within a "mock scanner". Task length is 12 minutes.

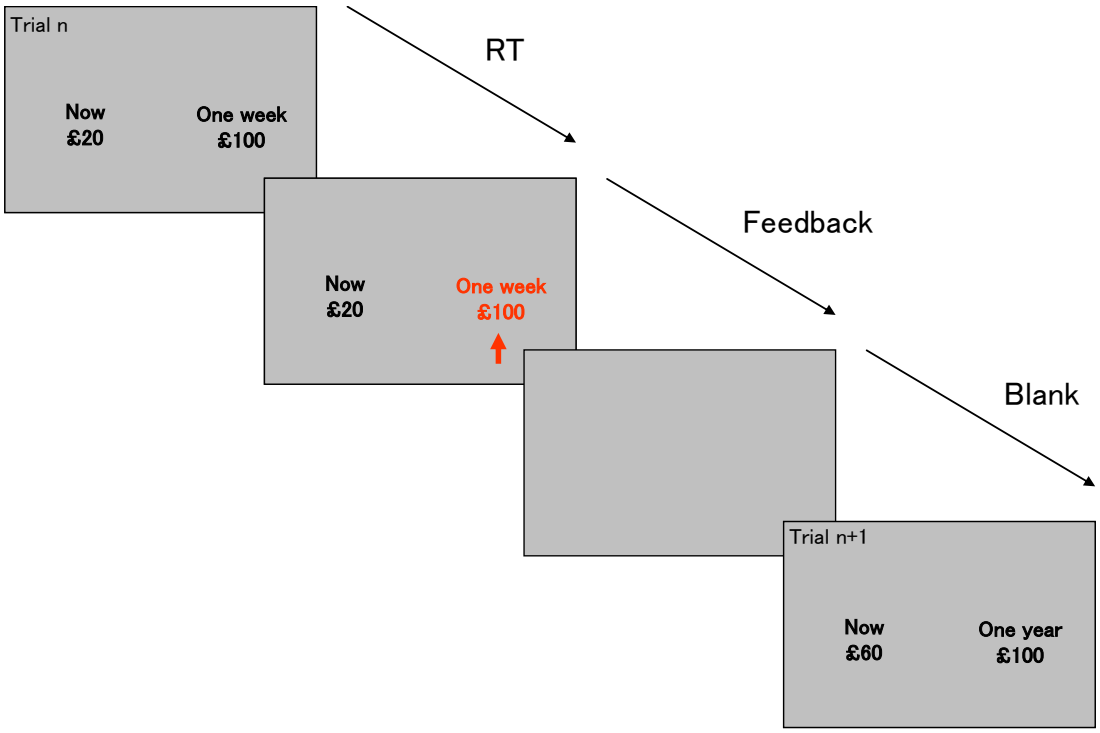



**Figure 7.1. Schematic representation of the temporal discounting (TD) task.** In the TD task, participants choose between an amount of money (£100) available after a delay of one week, one month and one year or a smaller amount of money available immediately (0-£100). For each participant, an algorithm is used to find values for the immediate option which are subjectively equivalent to the larger delayed option for each delay length, which ensures participants makes an equal number of immediate and delayed choices. Immediate options are presented on the left side of the screen and are selected by pressing a button placed under the right index finger. Delayed options are presented on the right side of the screen and are selected with the right middle finger. Each trial lasts for 4s, separated by blank screen interval of at least 8s (depending on the participant's reaction time) (inter-trial-interval: 12s).

### 7.2.3. Analysis of Performance Data

First, indifference points were calculated for each participant at each delay length. The indifference point as defined here is the midpoint value between the lowest selected immediate reward and the next highest offered reward value, and represents the subjective value of £100 after the specified delay. The subjective value of reward on the TD task can be described using a hyperbolic decay function, and estimated using the equation $V = A/(1 + kD)$, where V is the subjective value of a reward, A is size of the reward, D is the delay until reward receipt, and *k* is a constant which characterizes an individual's rate of discounting, and which is calculated by fitting a hyperbolic function to the indifference values for every

delay (Christakou et al., 2011; Richards et al., 1999). Larger *k* values indicate steeper discounting (Richards et al., 1999). Three-way ANCOVAs, controlling for non-significant differences in age, were performed between groups with *k* as the dependent measure to test for group differences in TD performance. We anticipated group differences in IQ, since ADHD is associated with low IQ (Bridgett & Walker, 2006). IQ was not covaried in the first instance as covarying for differences between groups that were not randomly selected violates ANCOVA assumptions (Miller & Chapman, 2001). However, supplementary analysis was performed covarying for IQ to test potential confounds.

### 7.2.4. fMRI Image Acquisition

The fMRI images were acquired at King's College London, Institute of Psychiatry's Centre for Neuroimaging Sciences on a 3T General Electric Signa Horizon HDx MRI scanner (GE Healthcare, UK) using the body coil for radio frequency transmission and a quadrature birdcage headcoil for radio frequency transmission and reception. In each of 22 non-contiguous planes parallel to the anterior–posterior commissure, 480 T2⁎-weighted MR images depicting BOLD contrast covering the whole brain were acquired with TE=30 ms, TR=1.5 s, flip angle=60°, in-plane voxel size=3.75 mm, slice thickness=5.0 mm, slice skip=0.5 mm). A whole-brain high resolution structural scan (inversion recovery gradient echo planar image) used for standard space normalisation was also acquired in the inter-commissural plane with TE=40 ms, TR=3 s, flip angle=90°, number of slices: 43, slice thickness=3.0 mm, slice skip=0.3 mm, in-plane voxel size=1.875 mm, providing complete brain coverage.

### 7.2.5. fMRI data

Data were first processed to minimize motion-related artefacts (Bullmore et al., 1999). A 3-D volume consisting of the average intensity at each voxel over the entire experiment was calculated and used as a template. The 3D image volume at each time point was then

realigned to this template by computing the combination of rotations (around the *x*, *y* and *z* axes) and translations (in *x*, *y* and *z*) that maximised the correlation between the image intensities of the volume in question and of the template (rigid-body registration). Following realignment, data were then smoothed using a Gaussian filter (full-width at half-maximum (FWHM) 7.2 mm) to improve the signal-to-noise ratio of the images (Bullmore et al., 1999). Following motion correction, global detrending (Bullmore et al., 2001; Bullmore et al., 1999), spin-excitation history correction and smoothing, time series analysis for each subject was conducted based on a previously published wavelet-based resampling method for fMRI data (Bullmore et al., 2001; Bullmore et al., 1999). At the individual-subject level, a standard general linear modelling approach was used to obtain estimates of the response size (beta) to each of the task conditions (delayed and immediate reward choices) against an implicit baseline. We first convolved the main experimental conditions with 2 Poisson model functions (peaking at 4 and 8s). We then calculated the weighted sum of these 2 convolutions that gave the best fit (least-squares) to the time series at each voxel. A goodness-of-fit statistic (SSQ ratio) was then computed at each voxel consisting of the ration of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by that of the squares due to the residuals (original time series minus model time series). The appropriate null distribution for assessing significance of any given SSQ ratio was established using a wavelet-based data re-sampling method (Bullmore et al., 2001) and applying the model-fitting process to the resampled data. This process was repeated 20 times at each voxel and the data combined over all voxels, resulting in 20 null parametric maps of SSQ rations for each subject, which were combined to give the overall null distribution of SSQ ratio. This same permutation strategy was applied at each voxel to preserve spatial correlation structure in the data. Individual SSQ ratio maps were then affine transformed into standard space, by first mapping the fMRI data onto a high-resolution inversion recovery

image of the same subject, and then by normalising onto a Talairach template. A group-level activation map was produced for each group for the experimental condition (delayed-immediate choices) by calculating the median observed SSQ ratios at each voxel in standard space across all subjects and testing them against the null distribution of median SSQ ratios computed from the identically transformed wavelet-resampled data (Brammer et al., 1997; Bullmore et al., 2001). ANCOVAs were conducted using randomization-based tests for voxel- or cluster-wise differences (Bullmore et al., 1999). The voxel-level threshold was first set to $P < 0.05$ to give maximum sensitivity and to avoid Type II errors. Next, a cluster-level threshold was computed for the resulting 3D voxel clusters in such a way as to produce less than one false positive 3D cluster per map. The necessary combination of voxel and cluster level thresholds was not assumed from theory but rather was determined by direct permutation for each dataset, giving excellent type-I and type-II error control (Bullmore et al., 2001). Cluster mass rather than a cluster extent threshold was used to minimize discrimination against possible small, strongly responding foci of activation (Bullmore et al., 1999). For comparisons between groups, one-way ANCOVA analyses with group as factor and head displacement in Euclidian 3-D space and age as covariates, were conducted using randomization-based tests for voxel or cluster-wise differences as described in detail elsewhere (Bullmore et al., 2001; Bullmore et al., 1999). Age was included as a covariate given established maturation effects on performance and neural function during TD (Christakou et al., 2011). For these between-group comparisons of the delayed-immediate contrast, less than one false activated cluster was expected at $p < .05$ for voxel and $p < .025$ for cluster comparisons. Analyses were repeated with IQ and *k* as additional covariates, to rule out the possibility that group differences resulted from differences in IQ or task performance.

Statistical measures of BOLD response (SSQ) for each participant were then extracted in each of the significant clusters and *post-hoc* least significance difference t-tests (correcting

for multiple comparisons) were conducted to identify between-group differences. To examine effects of medication of on brain activation, follow-up analyses were performed between medicated and unmedicated patients with ADHD as well as between controls and unmedicated ADHD using extracted BOLD response in clusters significant in the main analysis.

## 7.3. Results

### 7.3.1. Participant characteristics

There were no significant group differences in age, but IQ was significantly lower in ADHD (Table 7.1.).

**Table 7.1. Participant characteristics.**

| | **Controls** | **ADHD** | **OCD** | **Sig.** | |
|---|---|---|---|---|---|
| N | 20 | 26 | 20 | - | |
| Age | 15.3 (1.78) | 14.89 (1.71) | 15.75 (1.43) | F(2,63)=1.99, p=.145 | |
| IQ | 118.8 (11.99) | 102.57 (12.54) | 117.7 (13.36) | F(2,63)=12.63, p<.001 | C,OCD>ADHD |
| SDQ hyperactivity/inattention | 1.94 (1.63) | 7.31 (2.85) | 4.4 (3.03) | F(2,61)=22.5, p<.001 | ADHD>OCD>C |
| CY-BOCS | … | … | 22.32 (5.97) | | |
| Conner's T | … | 81.12 (7.55) | … | | |
| K mean | .016 (.013) | .046 (.042) | .027 (.031) | F(2,63)=5.1, p=.007 | ADHD>C,OCD |

*Abbreviations.* ADHD, attention-deficit/hyperactivity disorder; CYBOCS, Children's Yale-Brown Obsessive Compulsive Scale; IQ, intelligence quotient; OCD, obsessive/compulsive disorder; SDQ, strengths and difficulties questionnaire.

### 7.3.2. Performance data

ANCOVA showed that there was a significant between-group difference in *k* (F(2,62)=4.61, p=<.009) that was driven by steeper discounting in ADHD (mean *k*=.046 (*SD*=.042)) relative to control boys (mean *k*=.016 (SD=.013)) (p<.003) and at a trend-level relative to OCD boys (mean *k*=.027 (*SD*=.031)) (p<.07). After controlling for IQ, the ANCOVA remained significant at trend level (F(2,61)=2.99,p<.057).

### 7.3.3. Motion

ANOVA showed no group differences in mean displacement of x, y, z rotation and translation parameters (F(2,63)=1.6, p=.097).

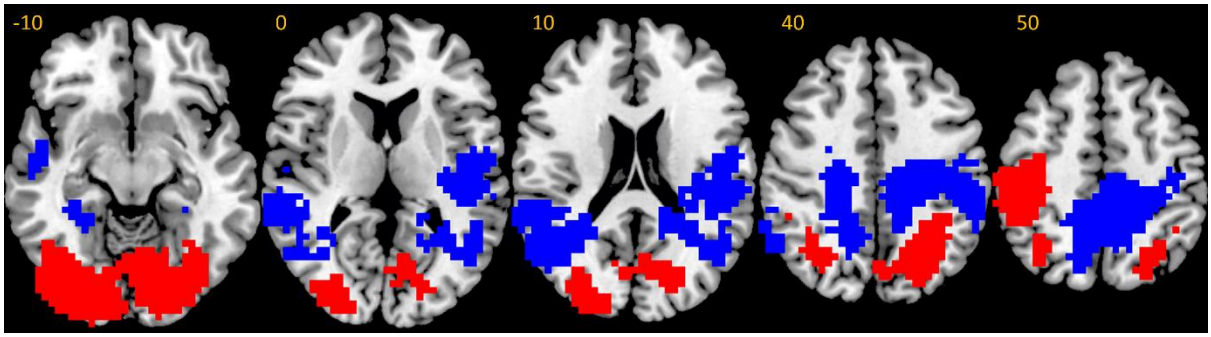
### 7.3.4. fMRI Data – Within-Group Activation Results

Controls activated bilateral postcentral gyrus, inferior parietal lobe, cerebellum and occipital lobe to delayed choices, and bilateral precentral gyrus, postcentral gyrus, supramarginal gyrus, middle temporal, superior temporal lobe, posterior insula to immediate choices (Figure 7.2.A.).

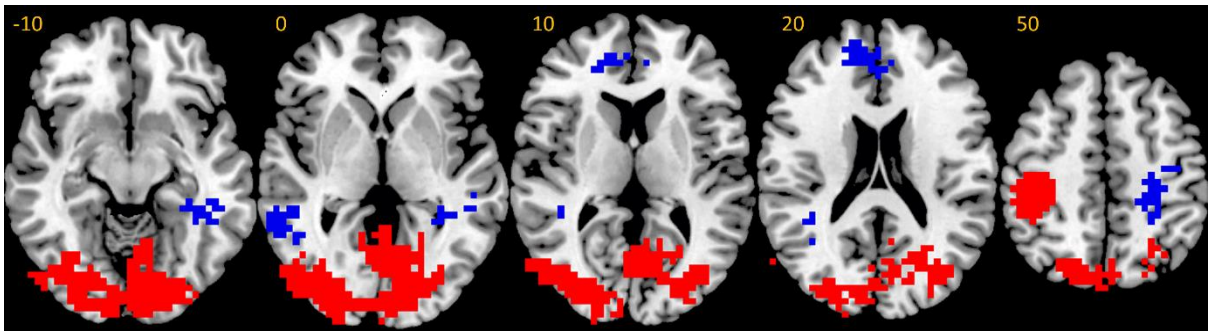
ADHD patients activated left precentral gyrus, postcentral gyrus, parietal lobe and bilateral cerebellum, occipital lobe to delayed choices, and medial prefrontal cortex, left caudate, precentral, postcentral gyrus, supramarginal gyrus, posterior insula, middle temporal, occipital lobe during immediate choices (Figure 7.2.B.).

OCD patients activated left precentral, postcentral gyrus, bilateral inferior parietal, supramarginal gyrus, occipital lobe, cerbellelum to delayed choices and bilateral medial prefrontal cortex, dorsolateral prefrontal cortex, posterior cingulate, middle temporal lobe, occipital lobe right caudate, precentral gyrus, postentral gyrus, superior parietal, superior temporal, hippocampus, amygdala to immediate choices (Figure 7.2.C.)

(a)




(b)




(c)

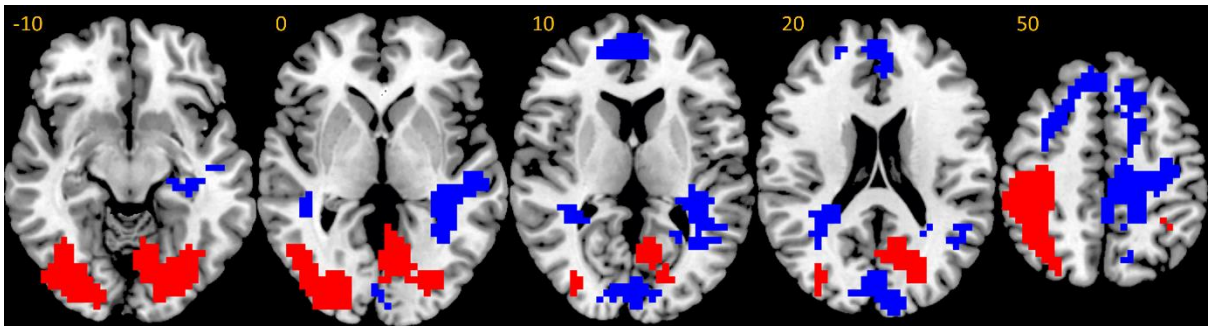



**Figure 7.2. Group activation maps for TD**. Axial slices showing within-group brain activation for the contrasts of delayed-immediate reward choices (red) and immediate-delayed reward choices (blue). (A) healthy controls, (B) ADHD patients (C) OCD patients. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the brain corresponds to the right side of the image. Data presented at voxel threshold $p<.05$ and cluster threshold $p<.05$.

### 7.3.5. Between-group differences

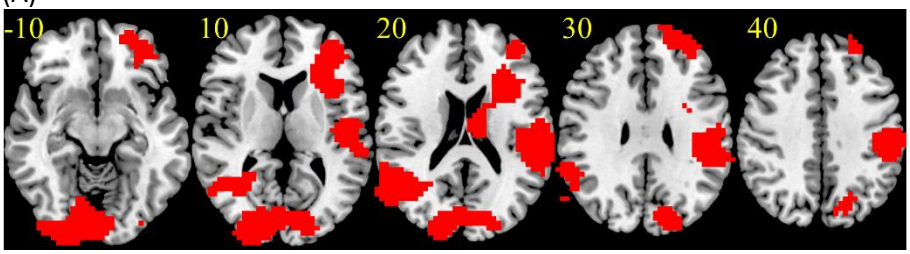
Whole-brain three-group ANCOVA analysis (controlling for age and motion) revealed that patients shared underactivation relative to controls in right IFG/anterior insula/caudate, right thalamus and bilateral occipital lobe/cerebellum during delayed relative to immediate trials, as well as left superior/middle temporal/supramarginal gyrus/fusiform gyrus and right

postcentral/superior temporal/supramarginal gyrus/posterior insula to immediate relative to delayed trials. OCD patients alone showed significantly reduced activation in right lOFC/vmOFC and rostrolateral prefrontal cortex(RLPFC)/DLPFC relative to controls (Table 7.2. & Figure 7.3.). All group difference clusters remained significant after controlling for IQ and *k* using whole-brain ANCOVA except for the cluster in left superior/middle temporal/supramarginal gyrus/occipital lobe, which was no longer significant after controlling for IQ.

Follow-up t-tests on extracted statistical BOLD activation in group difference clusters between medicated and unmedicated ADHD patients showed a significant difference in left temporal/parietal/occipital lobe activation ($t(24)=2.1$, $p<.046$), which was more active during immediate choices in medicated patients. In the unmedicated subgroup analysis on extracted BOLD activation, the cluster in thalamus no longer differed between ADHD and controls ($p=.112$) and the right AI/IFG/caudate cluster differed only at a non-significant trend ($p<.065$), presumably reflecting reduced power. All other group difference clusters remained significant.

There were no significant correlations between CY-BOCS scores and brain activation in the group difference clusters in the OCD patients, or between SDQ inattention/hyperactivity scale or CPRS-R scores and brain activation in ADHD patients ($p>.1$). Within controls there was a significant positive correlation between activation in the cerebellum/occipital lobe activation to delayed choices and *k* ($r(18)=.451$, $p=.046$), and there was a significant positive correlation between thalamus activation to delayed choices and *k* ($r(24)=.389$, $p=.049$) in ADHD patients, although these correlations did not survive correction for multiple comparisons (Benjamini & Hochberg, 1995). There were no correlations between *k* and brain activation in OCD patients ($p>.1$)

(A)




(B)

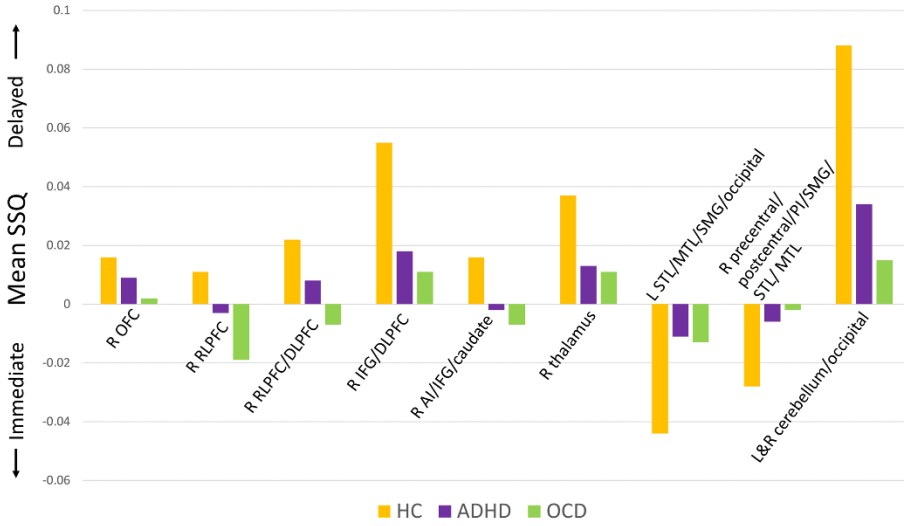



**Figure 7.3. ANCOVA results for the between-group differences in brain activation for contrast comparing delayed and immediate choices.** (A) Axial slices for the group activation maps for the three groups at P <.05 for voxel and P <.025. Red indicates significant between-group differences in activation in adolescents with ADHD and OCD relative to healthy comparison adolescents for delayed-immediate contrast. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the brain corresponds to the right side of the image. (B) Bar chart showing mean SSQ for each group in each cluster. Controls = orange, ADHD = purple, OCD = green.

**Table 7.2. ANCOVA differences in brain activation between adolescents with ADHD and OCD and healthy comparison adolescents.**

| Brain regions of activation | BA | TAL COORD | Voxels | Cluster p-value |
|---|---|---|---|---|
| **Delay>Immediate** | | | | |
| **Controls > OCD** | | | | |
| R OFC | 11 | 29,56,-18 | 41 | .011 |
| R RLPFC | 10/9 | 18,67,20 | 15 | .001 |
| R RLPFC/DLPFC | 46/10 | 29,56,26 | 54 | .001 |
| **Controls >ADHD,OCD** | | | | |
| R IFG/DLPFC | 45/46 | 33,44,4 | 105 | .003 |
| R anterior insula/IFG/caudate | 13/45 | 29,30,9 | 78 | .015 |
| R thalamus | | 11,-11,15 | 35 | .009 |
| L & R cerebellum/occipital lobe | 17/18/19 | -7,-78,-13 | 727 | .004 |
| **Immediate>Delay** | | | | |
| **Controls >ADHD,OCD** | | | | |
| R precentral/postcentral/posterior insula/SMG/STL/ MTL | 4/3/2/13/40/22/41/42/43 | 58,-15,26 | 332 | .01 |
| L STL/MTL/SMG/occipital lobe | 37/21/22/42/39/17/19 | -51,-56, 9 | 232 | .02 |

*Abbreviations:* ADHD, Attention-Deficit/Hyperactivity Disorder;; BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; MTL, middle temporal lobe; OCD, obsessive/compulsive disorder; OFC, orbitofrontal cortex; RLPFC, rostrolateral prefrontal cortex; SMG, supramarginal gyrus; STL, superior temporal lobe; TAL COORD, Talairach coordinates.

### 7.4. Discussion

This fMRI study investigated potentially shared and disorder-specific neurofunctional abnormalities in paediatric ADHD and OCD during TD. The findings show that both patient groups relative to controls, shared underactivation in key regions of self-control and temporal foresight (Noreika et al., 2013; Rubia, Halari, Christakou, et al., 2009) including right IFG, DLPFC, anterior insula, dorsal striatum and bilateral cerebellum during delayed choices. Only OCD patients showed underactivation during delayed choices relative to controls in right OFC which is responsible for goal-directed reward evaluation (Christakou et al., 2011; Hare et al., 2014) and in RLPFC region known to support prospection and planning (Burgess

et al., 2011; van den Heuvel et al., 2003). The findings suggest that key mechanisms associated with adaptive reward-related decision-making and temporal foresight during TD are impaired in both disorders, while OFC and RLPFC regions which have consistently been found to be dysfunctional in OCD, are exclusively impaired in OCD.

During TD, IFG, DLPFC, anterior insula, dorsal striatum and cerebellum are typically recruited more during the selection of larger delayed than immediate rewards (Christakou et al., 2011; Hare et al., 2014; Rubia, Halari, Christakou, et al., 2009). These regions are also activated when participants consider the negative long-term consequences of unhealthy foods (Hare, Camerer, & Rangel, 2009), smoking cigarettes (Kober et al., 2010), and illegal drug use (Volkow et al., 2010), suggesting a key role in self-control and temporal foresight (Carlisi et al., 2016; Rubia, Halari, Christakou, et al., 2009). Findings of decreased activation in these regions extend previous findings in ADHD during TD (Ortiz et al., 2015; Rubia, Halari, Christakou, et al., 2009), by showing that deficits are shared with patients with OCD during this task. Interestingly, it has been shown that IFG underactivation is disorder-specific in ADHD relative to OCD during inhibitory control, both in studies of switch and Stop tasks (Rubia, Cubillo, et al., 2010) and in a meta-analytic comparison of ADHD and OCD patients during motor and interference inhibition and switching tasks (Chapter 5). Although the IFG has been proposed to inhibit tempting immediate reward choices during TD (Carlisi et al., 2016; Noreika et al., 2013; Rubia, Halari, Christakou, et al., 2009), it is also implicated in working memory (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012; Nee et al., 2013), time estimation (Hart et al., 2012; Noreika et al., 2013; Rubia, Halari, Christakou, et al., 2009), attention (Hart et al., 2013; Rubia, Cubillo, et al., 2011) and reappraisal (Delgado et al., 2008; Giuliani et al., 2014; Kober et al., 2010; Volkow et al., 2010), cognitive strategies likely required for making delayed choices (Noreika et al., 2013; Rubia, Halari, Christakou, et al., 2009). These findings are also in line with reports that inhibitory control

and TD are mediated by neuroanatomically overlapping but functionally dissociable fronto-striatal neural circuits (Fineberg et al., 2014), and suggest that IFG underactivation in ADHD relative to OCD is task-specific to the context of inhibitory control, but not the context of TD.

Findings of largely shared dysfunction in right IFG, DLPFC, anterior insula, dorsal striatum and cerebellar regions during delayed choices in ADHD and OCD suggest that TD taps into a shared underlying transdiagnostic mechanism (Fineberg et al., 2014). A further implication of these findings is that shared neural deficits may potentially be normalised using the same psychological or psychopharmacological manipulation across both disorders. For instance, it was recently reported that TD performance was normalised in ADHD patients relative to controls following an acute dose of the SSRI fluoxetine. This was also associated with the up-regulation of activation in right IFG, anterior insula, and striatum, regions that was found to be underactive in ADHD and OCD in the current study (Carlisi et al., 2016). SSRIs including fluoxetine are first line treatment in OCD, and therefore it may be interesting to investigate whether shared underactivation in right hemisphere fronto-insula-striatal regions respond similarly to pharmacological manipulation across disorders.

Only OCD patients showed significantly reduced activation in right OFC during delayed choices relative to controls. The OFC is a key region for representing reward values (Hare et al., 2014), and receives signalling from both striato-limbic regions which process low-level reward properties and from DLPFC regions involved in temporal foresight and self-control, integrating both representations into a goal-directed reward valuation in order to guide long-sighted decision-making (Christakou et al., 2011; Hare et al., 2014). Adults with OCD show reduced DLPFC and OFC recruitment during affective reversal (Remijnse, Nielen, van Balkom, et al., 2006; Remijnse et al., 2009), suggesting that in OCD patients, alterations within this brain network may underlie the perseverative performance of undesired, goal-irrelevant behaviours due to a failure in flexibly updating reward associations (Remijnse et

al., 2009). Findings of reduced OFC in OCD is in line with predominantly orbito-striatal accounts of the disorder (Menzies et al., 2008), and extends these by implicating OFC dysfunction in choice impulsivity in OCD.

In RLPFC, controls showed greater activation during delayed choices while OCD patients showed greater activation during immediate choices. RLPFC has been implicated in episodic prospection (Burgess et al., 2011), planning (van den Heuvel et al., 2003), counterfactual thinking (Boorman, Behrens, & Rushworth, 2011), and representing abstract, temporally extended goals (Badre & D'Esposito, 2009), i.e. in processes involved in comparing competing options and considering their long-term outcomes. Results parallel the meta-analytic finding of disorder-specific increased RLPFC grey matter in paediatric OCD relative to paediatric ADHD (Chapter 5). Also, OCD patients show altered activity in this region during the resting state (Le Jeune et al., 2010) and symptom provocation (Rotge et al., 2008). Conventional treatments including CBT (Yamanishi et al., 2009) and SSRIs (Carey et al., 2004), as well as treatment with deep-brain stimulation (Le Jeune et al., 2010) and repetitive transcranial magnetic stimulation (Nauczyciel et al., 2014) normalize RLPFC cortex activity in OCD, and targeting this region (along with adjacent OFC) with neurofeedback training is associated with a decrease in OCD symptoms (Scheinost et al., 2013; Scheinost et al., 2014). However, the nature of the relationship between RLPFC alterations and OCD is poorly understood (Gruner, Anticevic, Lee, & Pittenger, 2016), and the findings of this study suggests that choice impulsivity may represent one mechanism linking established alterations in this region and OCD.

In line with previous research, this study found evidence of steeper discounting in ADHD relative to controls (Patros et al., 2016), but unlike a previous study by Sohn and colleagues (Sohn et al., 2014), this study did not find evidence of impulsive decision-making in OCD patients. However, the previous study used a far larger sample size. Owing to the focus on

more sensitive neural outcomes, the current study may have been underpowered to detect significant differences in the OCD group.

Limitations of the study include a lower IQ in the ADHD group, in light of evidence linking IQ to TD performance (Shamosh & Gray, 2008). However, lower IQ is typical for the population (Bridgett & Walker, 2006) and findings remained significant after covarying for IQ. Second, 54 % of patients were receiving psychostimulant medication which has been associated with increased fronto-striatal activation (Chapter 5) (Rubia, Alegria, Cubillo, et al., 2014), suggesting that the deficit findings in ADHD in fronto-striatal systems may have been mitigated by their stimulant treatment. However, significant clusters remained largely unchanged between medicated and unmedicated groups, and remained significant in sub-group comparisons of unmedicated patients.

To summarise, the study provides the first examination of the neurofunctional abnormalities during TD in OCD, as well as the first comparison of functional abnormalities during this task between ADHD and OCD patients. TD performance in both disorders was associated with a common pattern of underactivation in fronto-striatal-insula-cerebellum regions implicated in self-control and temporal foresight during delayed choices, suggesting that choice impulsivity in both disorders may partially represent a shared transdiagnostic mechanism. In addition, OFC and RLPFC were found to be disorder-exclusively underactivated in OCD relative to controls, in line with existing orbito-striatal accounts of OCD, and providing first time evidence for its involvement in choice impulsivity in the disorder.

## Chapter 8. Shared and disorder-specific neural dysfunction during decision-making under ambiguity in paediatric ADHD and OCD

### 8.1. Introduction

ADHD affects 3-8% of children worldwide and 4% of adults (Biederman et al., 2012), and is defined by age-inappropriate problems with inattention, impulsivity and hyperactivity (American Psychiatric Association, 2013).

OCD has a lifetime risk of 2-3% (Ruscio et al., 2010). The key symptoms are obsessions, defined as recurrent and intrusive thoughts (e.g., on themes of contamination, checking, orderliness and symmetry), and compulsions, i.e. repetitive, ego-dystonic and time-consuming behavioural and mental rituals (e.g., repetitive washing or checking) (American Psychiatric Association, 2013).

In the IGT, participants are presented with four decks of playing cards, and instructed to select cards, one at a time from any of the decks (Bechara et al., 1994; Bechara et al., 1999; Bechara et al., 1997). Each card is associated with a monetary win or loss. Disadvantageous decks provide big wins but even bigger losses, whereas advantageous decks provide smaller wins but even smaller losses resulting in an overall gain. Participants are not instructed as to the nature of the decks, and must establish over successive choices that choosing cards from the advantageous decks provides an overall net benefit. This is termed decision-making under ambiguity, as the outcomes and probabilities are not provided explicitly, and participants must learn to choose from the advantageous decks and avoid the disadvantageous card decks using feedback from previous trials (Christakou et al., 2009). The task therefore measures several cognitive functions, including the ability to learn the reinforcement contingencies of each deck, the inhibition of the immediate thrill associated with greater reward or risk taking in disadvantageous decks, and temporal foresight to understand the long-term future gain

associated with conservative advantageous choices (Christakou et al., 2009; Christakou, Gershman, et al., 2013; Dunn et al., 2006).

Both ADHD and OCD patients show performance deficits in the IGT (Garon et al., 2006; Grassi et al., 2015; Kim et al., 2015; Kodaira et al., 2012; Malloy-Diniz et al., 2007; Malloy-Diniz et al., 2008; Martoni et al., 2015; Miller et al., 2013; Starcke et al., 2010; Zhang, Dong, Ji, Tao, et al., 2015; Zhang, Dong, Ji, Zhu, et al., 2015). That is, unlike healthy controls, they fail to learn to choose from the advantageous decks and to avoid the disadvantageous ones. A failure to adequately learn and utilise behaviour-outcome contingencies to guide goal-directed behaviour may underlie respective impulsive and compulsive symptoms in ADHD and OCD (Gillan & Robbins, 2014; Starcke et al., 2010; Tripp & Wickens, 2008). However, it is unclear if the underlying neural dysfunctions associated with IGT performance are shared or disorder-specific in ADHD and OCD. Shared dysfunction would indicate that impairments in tasks measuring decision-making under ambiguity in IGT may represent an underlying transdiagnostic mechanism in both disorders, whereas disorder-specific findings would suggest that shared performance deficits result from distinct underlying neurocognitive mechanisms.

In this study, the aim was to conduct a direct comparison of neurofunctional abnormalities during performance of IGT task in paediatric ADHD and OCD. During decision-making, it was anticipated that both patients groups would demonstrate altered activity in the VS (Figee et al., 2011; Plichta & Scheres, 2014), but in prefrontal cortex it was anticipated that IFG underactivation would be more pronounced or disorder-specific to ADHD patients (Chapter 5) (Rubia, Cubillo, et al., 2010; Rubia, Cubillo, et al., 2011), while vmOFC dysfunction would be more pronounced or disorder-specific in OCD relative to ADHD patients (Chapter 7) (Menzies et al., 2008; Milad & Rauch, 2012; Remijnse, Nielen, Balkom, et al., 2006). During the outcome phase, it was anticipated that OCD patients would show decreased

mesolimbic responses to rewards, while ADHD patients were expected to show increased responses relative to healthy controls and patients with OCD (Admon et al., 2012; Becker et al., 2014; Marsh et al., 2015; Remijnse, Nielen, Balkom, et al., 2006; Strohle et al., 2008; von Rhein et al., 2015).

## 8.2. Methods and Materials

### 8.2.1. Participants

Fifty-six (16 ADHD, 20 OCD, 20 controls) right handed (Oldfield, 1971) male adolescents aged between 12-18 years participated, with an IQ>70 as measured by the WASI-R short form (Wechsler, 2008). ADHD boys met DSM-IV criteria for inattentive/hyperactive-impulsive combined subtype, as assessed using the standardized Maudsley diagnostic interview (Goldberg & Murray, 2006), and scored above clinical cut-off on the CPRS-R (Conners et al., 1998) and the inattention/hyperactivity scale of the SDQ (Goodman, 1997), and were recruited from local CAMHS. Eight ADHD boys were medication naïve, and 8 were receiving psychostimulant medication. Medicated ADHD patients underwent a 48 hour washout period prior to scanning. OCD boys were recruited from a national specialist clinic for child and adolescent OCD and local CAMHS and had clinical diagnoses of OCD, as assessed according to the ICD-10 criteria and the CY-BOCS (Scahill et al., 1997), Sixteen boys were medication naïve, while four were being treated with SSRI medication. Control participants had no diagnoses of any psychiatric conditions, and were recruited using local advertising.

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the local Research Ethics Committee (05/Q0706/275). Study details were explained to both child and guardian and written informed consent was obtained for all participants.

### 8.2.2. Iowa Gambling Task (IGT)

This study used computerized variant of the IGT (Christakou et al., 2009; Christakou, Gershman, et al., 2013). Participants were presented with four decks of cards (labelled A, B, C, and D) on a computer screen and were asked to select one of the decks by pressing with their right hand one of four buttons, which were arranged horizontally on an MR-compatible button box to correspond with the four decks. Participants completed 80 trials and were instructed to win as much money as possible and lose as little money as possible. Participants were not informed of how long the testing session would last or how many trials they would perform. There was a 50% probability of winning or losing on each deck. Decks A and B gave relatively large gains (£190, £200, or £210) but even larger losses (£240, £250, or £260), whereas decks C and D gave small gains (£90, £100, or £110) but even smaller losses (£40, £50, or £60). Consequently, A and B were led to overall loss and were therefore disadvantageous or "risky" decks, whereas C and D were advantageous "safe" decks, as they led to overall gain at the end of the task. Participants started with a "loan" of £2,000, which allowed for the accommodation of consecutive losses. The £2,000 loan and running total were presented at the bottom of the task display.

Trials were designed such that choice responses and outcomes were temporally separated, allowing the moment of decision and the moment of outcome evaluation to be hemodynamically decoupled, and consequently allowing for each to be examined separately. Each trial is divided as follows: (1) the choice phase, from the moment of presentation of the four decks until the execution of the choice (reaction time to button press; the maximum time allowed for a response was 6 s.); (2) a 6 s delay between choosing a deck and being presented with the outcome, during which the four decks remained on the screen, the deck chosen by the participant was superimposed with a wheel divided into 12 equal segments, and every 0.5 s, each consecutive segment filled with colour, counting down to outcome presentation; and

(3) the outcome evaluation phase, during which the outcome appears on screen for 3 s. Total trial length was 15 s, ending with a blank screen after outcome presentation that served as an implicit baseline in the fMRI analysis. If a response was omitted, the trial was programmed to progress directly to the blank screen for 9 s (making up the total trial time of 15 s). Omitted trials were excluded from the analysis (Figure 8.1.).

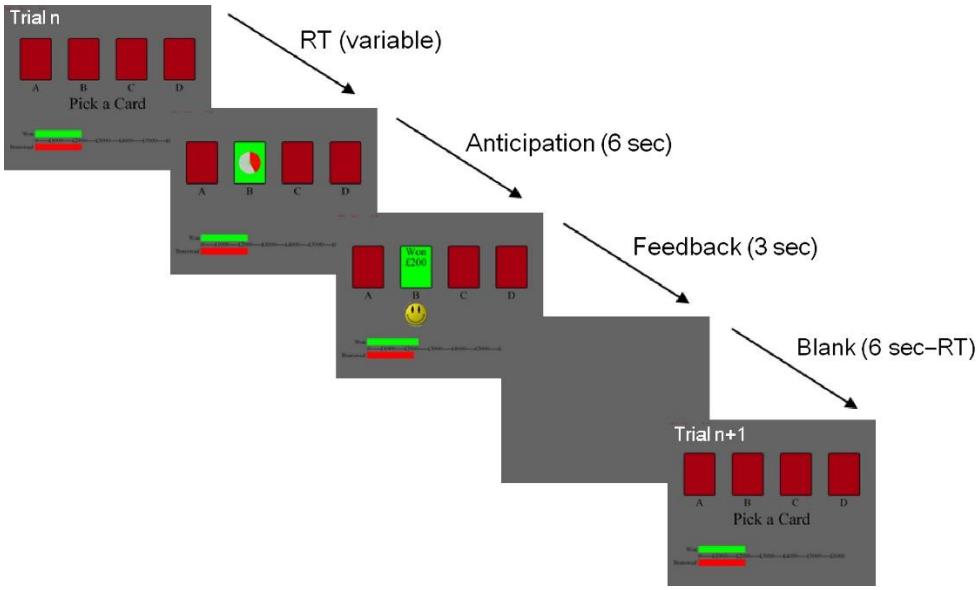



**Figure 8.1. Schematic representation of the Iowa gambling task (IGT).** On each trial of the IGT, participants chose from one of four decks by pressing the spatially corresponding button on an MR-compatible button box. The decision phase was followed by an anticipation phase (6s) before the outcome evaluation phase (3s) displayed the outcome of the decision (win/loss and magnitude). Each trial culminates with a blank screen that took the total trial duration to 15s. The loan (red bar) and the current running total (green bar) were presented at the bottom of the task display.

### 8.2.3. Analysis of Performance Data

IGT performance is summarized by the subject's net preference score, i.e., the number of cards picked from the disadvantageous decks (A + B) subtracted from the number if cards picked from the advantageous decks (C + D). A high positive net score denotes a preference for the advantageous relative to the disadvantageous decks, while very negative scores

indicate preference for the disadvantageous deck. Net score was calculated for all 80 trials and separately for each of four blocks of 20 trials.

Three-way ANCOVA (controlling for age) was used to compare groups on overall net score. To examine differences learning across task duration, 3 (group) X 4 (block) within-between repeated measures ANCOVA (controlling for age) was performed on net scores separated into four blocks of twenty trials.

### 8.2.4. fMRI Image Acquisition

The fMRI images were acquired at King's College London, Institute of Psychiatry's Centre for Neuroimaging Sciences on a 3T General Electric Signa Horizon HDx MRI scanner (GE Healthcare, UK) using the body coil for radio frequency transmission and a quadrature birdcage headcoil for radio frequency transmission and reception. In each of 22 non-contiguous planes parallel to the anterior–posterior commissure, 480 T2*-weighted MR images depicting BOLD contrast covering the whole brain were acquired with echo time TE=30 ms, TR=1.5 s, flip angle=60°, in-plane voxel size=3.75 mm, slice thickness=5.0 mm, slice skip=0.5 mm). A whole-brain high resolution structural scan (inversion recovery gradient echo planar image) used for standard space normalisation was also acquired in the inter-commissural plane with TE=40 ms, TR=3 s, flip angle=90°, number of slices: 43, slice thickness=3.0 mm, slice skip=0.3 mm, in-plane voxel size=1.875 mm, providing complete brain coverage.

### 8.2.5. fMRI Data Analysis

fMRI analysis was performed using non-parametric data analysis (XBAM). Data were first processed to minimize motion-related artefacts (Bullmore et al., 1999). A 3-D volume consisting of the average intensity at each voxel over the entire experiment was calculated and used as a template. The 3D image volume at each time point was then realigned to this

template by computing the combination of rotations (around the *x*, *y* and *z* axes) and translations (in *x*, *y* and *z*) that maximised the correlation between the image intensities of the volume in question and of the template (rigid-body registration). Following realignment, data were then smoothed using a Gaussian filter (full-width at half-maximum (FWHM) 7.2 mm) to improve the signal-to-noise ratio of the images (Bullmore et al., 1999). Following motion correction, global detrending , (Bullmore et al., 2001; Bullmore et al., 1999) spin-excitation history correction and smoothing, time series analysis for each subject was conducted based on a previously published wavelet-based resampling method for fMRI data (Bullmore et al., 2001; Bullmore et al., 1999). At the individual-subject level, a standard general linear modelling approach was used to obtain estimates of the response size (beta) to each of the task conditions against an implicit baseline. We first convolved the main experimental conditions with 2 Poisson model functions (peaking at 4 and 8s). We then calculated the weighted sum of these 2 convolutions that gave the best fit (least-squares) to the time series at each voxel. A goodness-of-fit statistic (SSQ ratio) was then computed at each voxel consisting of the ration of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by that of the squares due to the residuals (original time series minus model time series). The appropriate null distribution for assessing significance of any given SSQ ratio was established using a wavelet-based data re-sampling method (Bullmore et al., 2001) and applying the model-fitting process to the resampled data. This process was repeated 20 times at each voxel and the data combined over all voxels, resulting in 20 null parametric maps of SSQ rations for each subject, which were combined to give the overall null distribution of SSQ ratio. This same permutation strategy was applied at each voxel to preserve spatial correlation structure in the data. Individual SSQ ratio maps were then affine transformed into standard space, by first mapping the fMRI data onto a high-resolution inversion recovery image of the same subject, and then by normalising onto a

Talairach template. A group-level activation map was produced for each group for the experimental conditions (disadvantageous-advantageous choices and wins-losses) by calculating the median observed SSQ ratios at each voxel in standard space across all subjects and testing them against the null distribution of median SSQ ratios computed from the identically transformed wavelet-resampled data (Brammer et al., 1997; Bullmore et al., 2001). ANCOVAs were conducted using randomization-based tests for voxel- or cluster-wise differences (Bullmore et al., 1999). The voxel-level threshold was first set to $P < 0.05$ to give maximum sensitivity and to avoid Type II errors. Next, a cluster-level threshold was computed for the resulting 3D voxel clusters in such a way as to produce less than one false positive 3D cluster per map. The necessary combination of voxel and cluster level thresholds was not assumed from theory but rather was determined by direct permutation for each dataset, giving excellent type-I and type-II error control (Bullmore et al., 2001). Cluster mass rather than a cluster extent threshold was used to minimize discrimination against possible small, strongly responding foci of activation (Bullmore et al., 1999). For the between-group comparisons, one-way ANCOVA analyses with group as factor and head displacement in Euclidian 3-D space and age as covariates. Age was included as a covariate given established maturation effects on performance and neural function during IGT (Christakou, Gershman, et al., 2013). For these between-group comparisons of the delayed-immediate contrast, less than one false activated cluster was expected at $p < .05$ for voxel and $p < .004$ for cluster comparisons for the choice phase and $p < .0045$ for the outcome phase.

Additional analyses were performed using regions of interest (ROI) based on a priori hypotheses. A single ROI search space was based on regions implicated in IGT and reward/punishment processing and expected to differ between patient groups. This included bilateral orbitofrontal cortex, medial frontal gyrus, inferior frontal gyrus (opercularis), inferior frontal gyrus (triangularis), insula, putamen, caudate and nucleus accumbens.

Regions were extracted from the Harvard-Oxford atlas using FSL (Kennedy et al., 1998; Makris et al., 1999) and nonlinearly converted from Montreal Neurological Institute coordinates into Talairach coordinates using the MNI2TAL program (ftp://ftp.mrc-cbu.cam.ac.uk/pub/imaging/MNI2tal/mni2tal.m) for use in XBAM. Within this search space, less than one false activated cluster was expected at $p<.05$ for voxel and $p<.02$ for cluster comparisons during decision and outcome phases.

Statistical measures of BOLD response (SSQ) for each participant were then extracted in each of the significant clusters and post-hoc least significance difference t-tests (correcting for multiple comparisons) were conducted to identify between-group differences.

## 8.3. Results

### 8.3.1. Participant characteristics

There were no significant group differences in age, but IQ was significantly lower in ADHD (Table 8.1.).

**Table 8.1. Participant characteristics.**

| | Controls | ADHD | OCD | Sig. | |
|---|---|---|---|---|---|
| N | 20 | 16 | 20 | - | |
| Age | 15.17 (1.98) | 14.61 (1.87) | 15.76 (1.43) | F(2,53)=1.89, p=.162 | |
| IQ | 119.65 (11.9) | 107.56 (12.89) | 117.7 (13.36) | F(2,53)=4.48, p=.016 | C,OCD>ADHD |
| SDQ hyperactivity/inattention | 2 (1.71) | 8.5 (1.21) | 4.4 (3.03) | F(2,51)=37.54, p=<.001 | ADHD>OCD>C |
| CY-BOCS | … | … | 22.32 (5.97) | | |
| Conner's T | … | 80.94 (7.65) | … | | |
| Net score | 10.45 (24.45) | -2.69 (18.7) | 4.75 (17.4) | F(2,53)=1.8, p=.172 | |

*Abbreviations.* ADHD, Attention-Deficit/Hyperactivity Disorder; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; IQ, intelligence quotient; OCD, obsessive/compulsive disorder; SDQ, strengths and difficulties questionnaire.

### 8.3.2. Performance data

A 3 (group) X 4 (block) within-between repeated measures ANCOVA (controlling for age) showed no main effect of group in overall net score ($F(1,52)=1.59$, p=.213), no significant main effect of block ($F(2.65, 137.87)=.737$, p=.516), and no significant group by block interaction effect (F(5.3, 138.87)=1.57, p=.169). (Table 8.1.). Findings were unchanged after controlling for IQ.

### 8.3.3. Movement

ANOVA showed no group differences in mean Euclidean displacement of x, y, z parameters (F(2,53)=1.58, p=.216).

### 8.3.4. Between-group differences

For the choice phase, a whole-brain three-group ANCOVA analysis (controlling for age and motion) revealed that ADHD and OCD patients showed shared dysfunction in PCC/precuneus/SMA relative to controls. In controls, this cluster was more active to disadvantageous choices, while in patients it was more active during advantageous choices. Within the ROI search mask, significant group differences were found in left VS and vmOFC. Within the left VS, underactivation during safe choices was shared in both patient groups relative to controls. Within the vmOFC, underactivation during advantageous choices was disorder-specific to patients with OCD relative to both controls and patients with ADHD, who did not differ (Table 8.2., Figures 8.2. & 8.3.).

For the outcome evaluation phase, a whole-brain three-group ANCOVA analysis (controlling for age and motion) revealed that ADHD and OCD patients showed shared underactivation during win outcomes in the precuneus relative to controls, as well as shared underactivation during losses in rostral MPFC. Within the ROI search space, shared-dysfunction was found in bilateral putamen/caudate. In left putamen/caudate, shared underactivation to wins was found in ADHD and OCD patients groups relative to controls. In right putamen/caudate, ADHD patients showed disorder-specific dysfunction relative to controls and patients with OCD, who did not differ significantly. Patients with ADHD showed greater activation to losses, while controls showed greater activation to wins (Table 8.2., Figures 8.4. & 8.5.).

After controlling for IQ, findings in the vmOFC, VS, and left putamen remained significant at the standard threshold (less than one error cluster). Findings in the SMA/PCC/precuneus ($p=.009$), right putamen ($p=.046$), precuneus ($p=.016$) and rostral MPFC ($p=.027$) remained significant only at a relaxed cluster thresholds of $p<.05$.

**Table 8.2. ANCOVA differences in brain activation between adolescents with ADHD and OCD and healthy comparison adolescents.**

| Brain regions of activation | BA | TAL COORD | Voxels | Cluster p-value |
|---|---|---|---|---|
| **Advantageous>disadvantageous choices** | | | | |
| **Controls > ADHD, OCD** | | | | |
| VS[1] | | -11,4,4 | 35 | .014 |
| **Controls, ADHD > OCD** | | | | |
| vmOFC[1] | 11 | 4,41,-13 | 28 | .011 |
| **Disadvantageous>advantageous choices** | | | | |
| **Controls > ADHD, OCD** | | | | |
| SMA/PCC/precuneus | 4/23/5 | 29,-26,48 | 138 | .003 |
| **Wins>losses** | | | | |
| **Controls >ADHD, OCD** | | | | |
| L&R precuneus | 19/7 | 36,-74,37 | 185 | .002 |
| L putamen[1] | | -22,0,9 | 44 | .009 |
| **Controls, OCD >ADHD** | | | | |
| R putamen[1] | | 22,-4,9 | 48 | .012 |
| **Losses>wins** | | | | |
| **Controls >ADHD, OCD** | | | | |
| MPFC | 32 | -4,48,9 | 121 | .004 |

*Abbreviations:* ADHD, Attention-Deficit/Hyperactivity Disorder; BA, Brodmann area; MPFC, medial prefrontal cortex; OCD, obsessive/compulsive disorder; PCC, posterior cingulate; SMA, supplementary motor area; TAL COORD, Talairach coordinates; vmOFC, ventromedial prefrontal cortex; VS, ventral striatum.

[1]Significant in ROI search space.

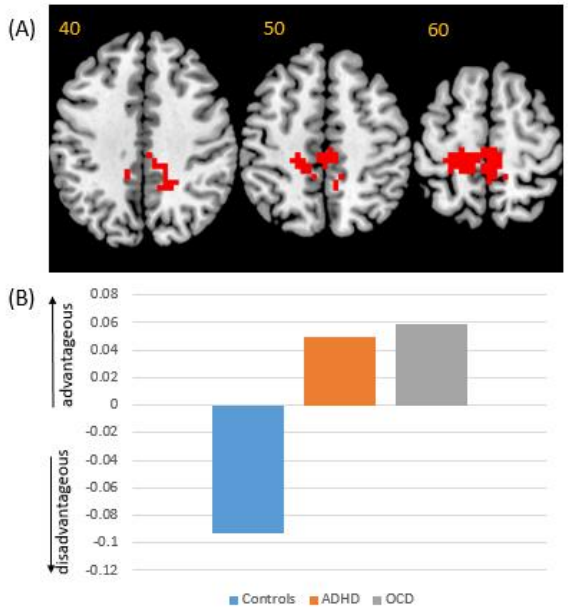



**Figure 8.2. ANCOVA results for the between-group differences in brain activation for contrast comparing advantageous and disadvantageous choices.** (A) Axial slices for the group activation maps for the three groups at P <.05 for voxel and P <.004 for cluster comparisons. Red indicates significant between-group differences in activation in adolescents with ADHD and OCD relative to healthy comparison adolescents. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the brain corresponds to the right side of the image. (B) Bar chart showing mean SSQ for each group in each cluster. Controls = blue, ADHD = orange, OCD = grey.

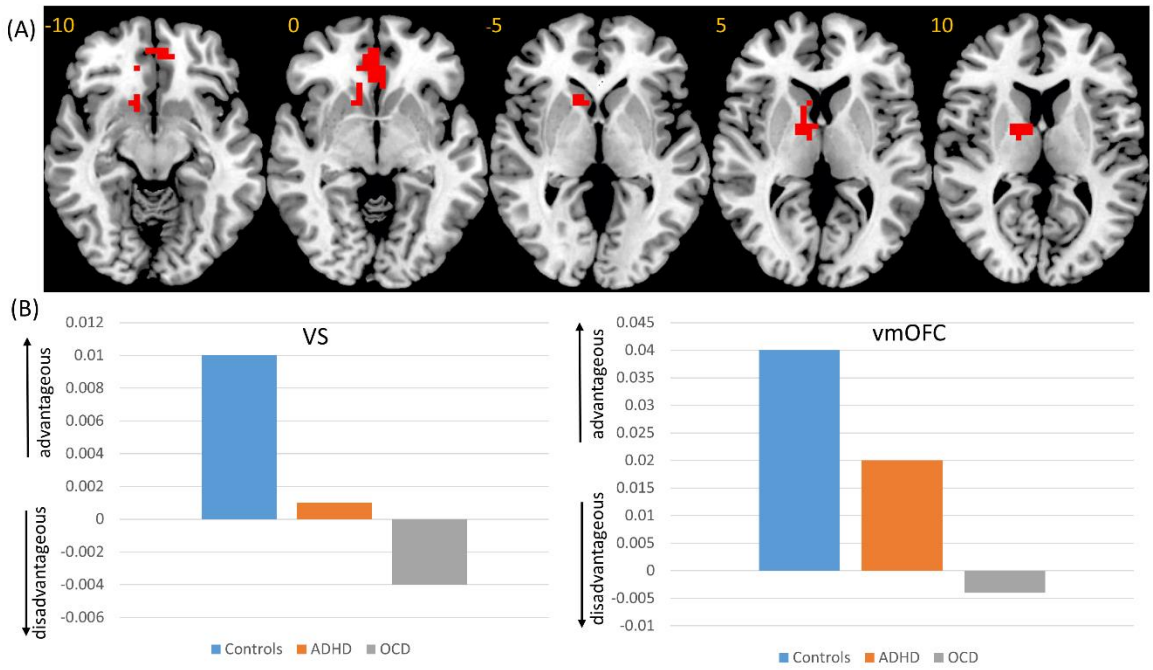



**Figure 8.3. ANCOVA results for the between-group differences in brain activation for contrast comparing advantageous and disadvantageous choices within the ROI search space.** (A) Axial slices for the group activation maps for the three groups at P <.05 for voxel and P <.02 for cluster comparisons. Red indicates significant between-group differences in activation in adolescents with ADHD and OCD relative to healthy comparison adolescents. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the brain corresponds to the right side of the image. (B) Bar chart showing mean SSQ for each group in each cluster. Controls = blue, ADHD = orange, OCD = grey.

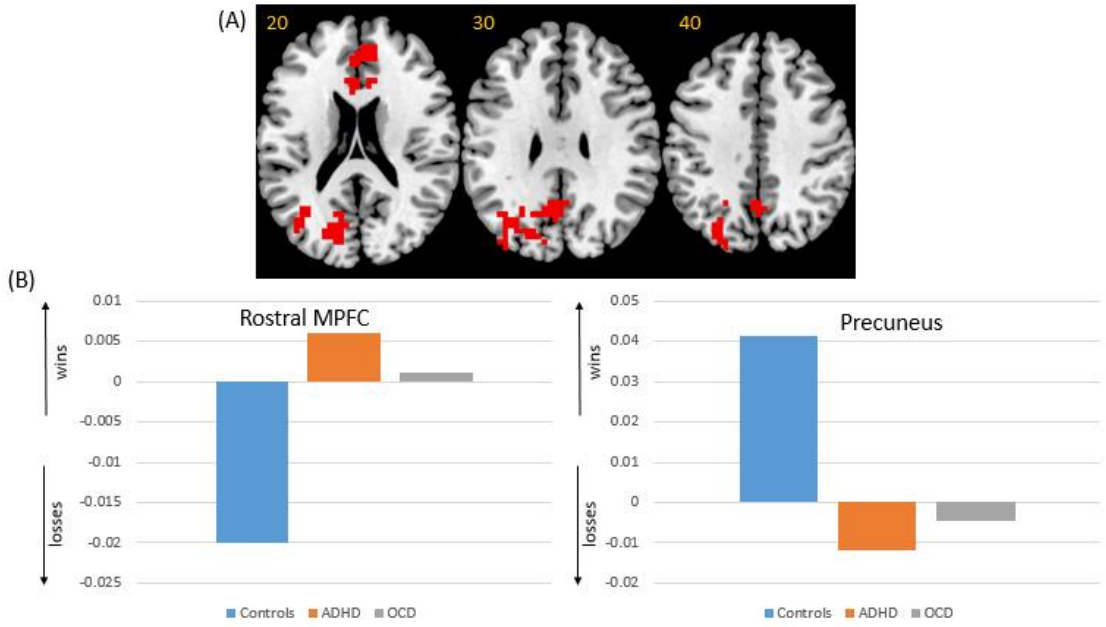



**Figure 8.4. ANCOVA results for the between-group differences in brain activation for contrast comparing win and loss outcomes.** (A) Axial slices for the group activation maps for the three groups at P <.05 for voxel and P <.0045 for cluster comparisons. Red indicates significant between-group differences in activation in adolescents with ADHD and OCD relative to healthy comparison adolescents. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the brain corresponds to the right side of the image. (B) Bar chart showing mean SSQ for each group in each cluster. Controls = blue, ADHD = orange, OCD = grey.

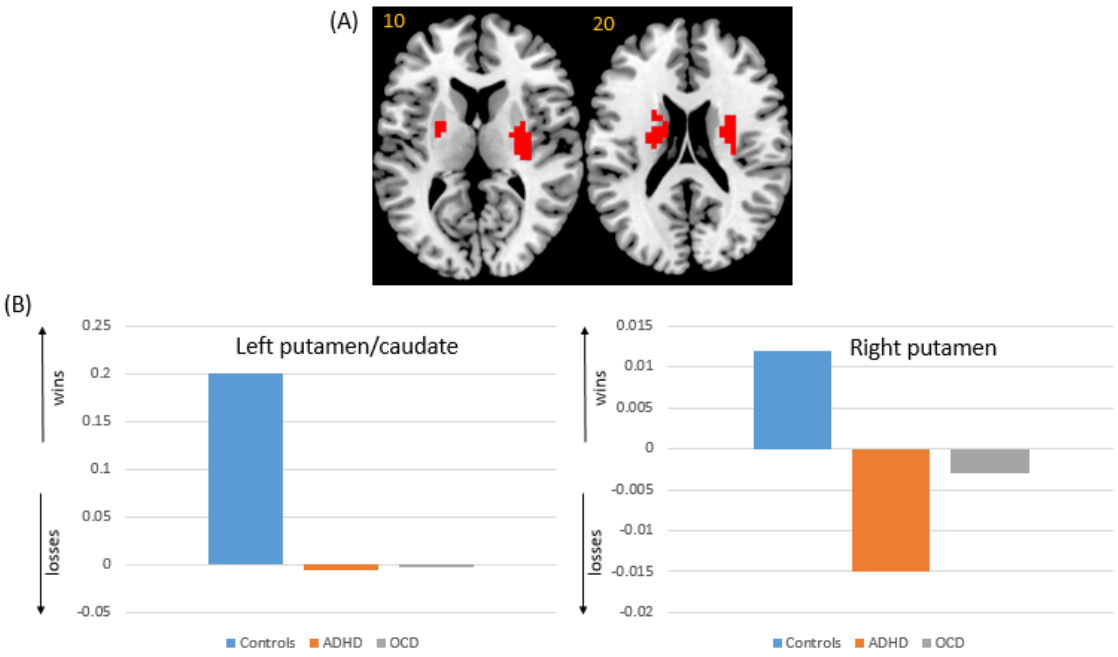



**Figure 8.5. ANCOVA results for the between-group differences in brain activation for contrast comparing win and loss outcomes within the ROI search space.** (A) Axial slices for the group activation maps for the three groups at P <.05 for voxel and P <.02 for cluster comparisons. Red indicates significant between-group differences in activation in adolescents with ADHD and OCD relative to healthy comparison adolescents. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the brain corresponds to the right side of the image. (B) Bar chart showing mean SSQ for each group in each cluster. Controls = blue, ADHD = orange, OCD = grey.

### 8.3.5. Exploratory brain-behaviour and brain-performance correlations

Statistical BOLD response from regions that showed significant group differences were extracted, and correlated with task performance and symptom scores within each group.

Within controls, net score was significantly correlated with activation in VS (r(18)=.502, p=.024) and vmOFC (r(18)=.565, p=.009) during the choice phase, such that greater activation during advantageous relative to disadvantageous choices was associated with a greater proportion of advantageous choices. In ADHD and OCD patients there were significant correlations between precuneus activation and net score. However, in patients with ADHD, greater activation to disadvantageous choices was associated with a higher net

score (r(14)=-.574, p=.02), while in OCD patient greater activation to advantageous choices was associated with a higher net score (r(18)=.582, p=.007). Only the latter finding survived correction for multiple comparisons (Benjamini & Hochberg, 1995)

There were no significant correlations between symptoms and brain activation within either ADHD or OCD patient groups (p>.1)

**8.4. Discussion**

The study investigated potentially shared and disorder-specific neural abnormalities during the IGT in adolescent ADHD and OCD patients. During the decision-making phase, shared dysfunction was found in the PCC/precuneus/SMA, which was more active during disadvantageous choices in controls but more active during advantageous choices in patients, and in the VS, which was underactive in both patient groups during advantageous choices. Disorder-specific choice related activation was found in the vmOFC, which was underactive in OCD patients relative to both controls and ADHD patients during advantageous choices. Shared and disorder-specific dysfunction was also found in the outcome phase. Shared underactivation to losses was found in MPFC, while shared underactivation to wins was found in left putamen/caudate and precuneus. Disorder-specific dysfunction was found in right putamen/caudate, which activated more to wins in controls but more to losses in patients with ADHD.

Adolescent patients with OCD showed disorder-specific underactivation in vmOFC during advantageous choices. In the IGT, the vmOFC is the primary frontal region associated with task performance, based on both the lesion and neuroimaging literature (Bechara et al., 1994; Bechara et al., 1999; Bechara et al., 1997; Christakou et al., 2009; Christakou, Gershman, et al., 2013; Ernst, Kimes, et al., 2003; Glascher et al., 2012; Lawrence, Jollant, O'Daly, Zelaya, & Phillips, 2009; Li, Lu, D'Argembeau, Ng, & Bechara, 2010; Premkumar et al., 2008;

Tanabe et al., 2007), and, in the current study, greater vmOFC activation was associated with better task performance in healthy controls. The vmOFC is a key structure for flexible emotional learning, in particular re-evaluating behaviour- and stimulus-reward contingencies (Remijnse, Nielen, Balkom, et al., 2006), and for guiding decision-making by encoding prospective values for available options based on both low-level incentive salience properties and higher-order knowledge of environment structure and long-term goals in order to guide long-sighted goal-directed decision (Gillan et al., 2014; Hampton, Bossaerts, & O'Doherty, 2006; Hare et al., 2009; Hare, Malmaud, & Rangel, 2011). The vmOFC has been consistently implicated in OCD, and abnormal activity is reported at rest, as well as during symptom provocation, emotion and cognitive tasks (Banca et al., 2015; Menzies et al., 2008; Whiteside et al., 2004; Woolley et al., 2008). The current results extend these previous findings, as well as findings of disorder-specific dysfunction in ventral MPFC in sustained attention and TD tasks relative to ADHD (Chapters 6 and 7), by implicating vmOFC dysfunction in decision-making under ambiguity in OCD, and moreover by demonstrating disorder-specificity relative to ADHD.

The vmOFC is closely interconnected with VS and limbic brain regions as part of dopaminergic cortical-subcortical mesolimbic reward networks (Figee et al., 2011; Furukawa et al., 2014; Hampton et al., 2006; Hare et al., 2009; Menzies et al., 2008; Remijnse, Nielen, van Balkom, et al., 2006; Remijnse et al., 2009), and in the current study the VS was underactive during advantageous choices in both patient groups relative to controls, while activation in controls correlated positively with task performance. The VS responds in a bottom-up manner to a number of reinforcers including monetary reward (Frangou, Kington, Raymont, & Shergill, 2008; Tanabe et al., 2007), and contributes information about motivational properties and magnitude of available rewards, thus initially biasing decision-making towards impulsive, immediate or larger but riskier rewarding actions (Kuhnen &

Knutson, 2005; Matthews, Simmons, Lane, & Paulus, 2004). However, during learning dopamine cell responses within the VS are shifted from established reinforcers to cues or behaviours which predict rewarding outcomes, and VS responses to advantageous choices in controls may therefore represent the net positive expected value established in the VS associated with choosing from the advantageous decks (Frank, Santamaria, O'Reilly, & Willcutt, 2007; Furukawa et al., 2014; Keeler, Pretsell, & Robbins, 2014; Kollins & Adcock, 2014; Tripp & Wickens, 2008; Tripp & Wickens, 2009).

In ADHD, reduced VS activation is in line with studies using MID tasks which find reduced VS to cues which predict rewards (Edel et al., 2013; Hoogman et al., 2011; Kappel et al., 2015; Plichta & Scheres, 2014; Plichta et al., 2009; Scheres et al., 2007; Stoy et al., 2011; Strohle et al., 2008), as well as findings from a study that used a TD task, in which adult patients with ADHD showed reduced VS activity when deciding between sooner and later rewards (Plichta et al., 2009). Findings of VS hypoactivation can be interpreted within the dopamine transfer deficit theory of ADHD, which suggests that the dopamine response in the VS to previously neutral cues or behaviours which are now associated with reward is disrupted, such that motivational or incentive salience features and underlying VS activation that these cues take on in controls are absent in ADHD (Furukawa et al., 2014; Tripp & Wickens, 2008; Tripp & Wickens, 2009). In the IGT therefore, failures in representing the reinforcement history of each decks within the VS may lead to impairments in patients with ADHD in making decisions associated with long-term beneficial outcomes.

Orbito-striatal models dominate the OCD literature (Graybiel & Rauch, 2000; Menzies et al., 2008; Milad & Rauch, 2012). OCD patients show alterations in vmOFC-striatal circuitry during symptom provocation, as well as during reward reversal and fear extinction studies requiring updating of reward-punishment contingencies, and decreased vmOFC but increased striatal GMV is reported in meta-analyses of the disorder (Eng, Sim, & Chen, 2015b; Radua

& Mataix-Cols, 2009; Radua et al., 2010). Previous research has shown reduced VS response to cues which predict reward in OCD (Figee et al., 2013; Figee et al., 2011; Marsh et al., 2015), but increased VS and dorsal striatal responses during symptom provocation and habitual responding in OCD patients (Baioui et al., 2013; Banca et al., 2015; Gillan et al., 2015; Mataix-Cols et al., 2004), and alterations in VS mediated salience and motivation related processes may underlie performance of OCD related behaviours at the expense of goal-related behaviour in the disorder (Figee et al., 2011; Gillan & Robbins, 2014; Gillan, Robbins, Sahakian, van den Heuvel, & van Wingen, 2016). Imbalance or disruption within orbito-striatal pathways in OCD may therefore result in increased bottom-up striatal influence over behaviour at the expense of controlled goal-directed actions requiring adequate fronto-striatal integration, for example increased habit-like or immediately rewarding but ultimately detrimental compulsions (Figee et al., 2011; Gillan & Robbins, 2014), or, relatedly, a disruption of reward contingency (re-)learning (Remijnse, Nielen, Balkom, et al., 2006).

The findings of this study thus support vmOFC-striatal deficits in OCD, and furthermore extend these findings by showing that these are disorder-specific relative to ADHD with respect to the ventromedial orbitofrontal part of the network, while the VS part may be a transdiagnostic feature of both disorders in the context of reward related decision-making.

Patient groups shared reduced activation to wins in left putamen and in precuneus and to losses in MPFC. In the IGT, outcome evaluation is important for providing a learning signal to guide future decisions (Bechara et al., 1994; Bechara et al., 1999; Bechara et al., 1997; Christakou et al., 2009; Christakou, Gershman, et al., 2013), a process closely linked with putamen and MPFC activity (Liu, Hairston, Schrier, & Fan, 2011). Underactivation to losses in the MPFC is in line with previous findings of reduced MPFC localised feedback-related negativity (FRN) to monetary loss in ADHD patients (Gonzalez-Gadea et al., 2016). Although this study did not examine group difference in neural encoding of prediction errors,

findings of reduced MPFC and striatal sensitivity to losses and wins, respectively, are broadly speaking in line with computational models and neuroimaging data suggesting reduced representation of reward-prediction errors (differences in expected and actual outcomes) in mesolimbic pathways in ADHD (Hauser et al., 2014; Silvetti, Wiersema, Sonuga-Barke, & Verguts, 2013). Reduced MPFC and striatal responsivity during the outcome phase is in line with previous fMRI studies in adults with OCD (Becker et al., 2014; Figee et al., 2011; Remijnse, Nielen, Balkom, et al., 2006; Remijnse et al., 2009), as well as with findings of reduced MPFC GMV and functional activation during inhibitory control (Chapter 5), and consistent with accounts suggesting that OCD patients have deficits using external feedback to learn new task rules, which may underlie perseverative compulsive behaviours that are continued in spite of ultimately negative consequences (Nielen, den Boer, & Smid, 2009; Olley, Malhi, & Sachdev, 2007).

An unexpected finding was that PCC was more active during disadvantageous choices in controls during decision-making, but more active during advantageous decisions in both patient groups. The PCC is often active during decision-making tasks, and is closely implicated in reward processing, attention and in the DMN where it may underlie memory, prospection and cognitive deliberation (Liu et al., 2011; Raichle, 2015; Raichle et al., 2001). Abnormalities in posterior DMN are shared in paediatric ADHD and OCD, and abnormal activation may result from underlying differences in baseline activation, or a failure in the integration of DMN with task-positive networks to support goal-directed deliberation and prospection of possible outcomes during decision-making. Alternatively, the PCC is implicated in initiation of explorative behaviour during decision-making, and increased activation during choices of disadvantageous choices in controls might represent consideration of alternative choices, for example to re-check expected outcome contingencies, or to gamble that they may receive the large win outcome associated with the

disadvantageous decks (Pearson, Heilbronner, Barack, Hayden, & Platt, 2011). However, these hypotheses are post-hoc and further study might further elucidate the role of the PCC in decision-making in paediatric ADHD and OCD.

Also unexpected was that, unlike in some previous studies using the MID, patients with ADHD did not exhibit increased activation to wins in vmOFC or VS, and instead showed disorder-specific increased activation to losses in right putamen. A lack of increased reactivity to wins might reflect differences between the MID and IGT. For instance, in the MID contingencies between cues and reward outcomes do not need to be learned, whereas outcome evaluation in the IGT is important for learning the outcomes associated with each deck, and qualitatively different orbito-striatal signalling may be involved in passive reward receipt and active outcome evaluation (Liu et al., 2011). Increased right putamen activation to losses relative to wins might suggest alternative outcome signalling in ADHD, although a caveat is that ADHD showed a non-significant greater preference for the disadvantageous deck relative to controls and patients with OCD, and therefore losses were on average of a greater magnitude in ADHD.

It was anticipated that the IFG would be underactive in ADHD patients, as this region has been shown to be underactive in ADHD during decision-making in TD tasks, as well as in inhibitory control, sustained attention and timing tasks (Chapters 5,6,7) (Hart, Marquand, et al., 2014; Hart et al., 2012; Rubia, Halari, Christakou, et al., 2009). Furthermore, it was hypothesised that this region would be disorder-specific in its underactivation in ADHD relative to OCD as observed in previous studies (Rubia, Cubillo, et al., 2010). However, there were no group differences in IFG activation. The IFG may take on a more important role after participants have learned the task, and temporal foresight and self-control is required to direct choices towards options with small but ultimately net positives and away from tempting potential large rewards (Dunn et al., 2006). Although fMRI studies have reported

IFG during decision-making (Christakou, Gershman, et al., 2013; Cousijn et al., 2013; Power, Goodyear, & Crockford, 2012; Tanabe et al., 2007), studies of lesion patients suggest that the vmOFC, but not the IFG, is crucial for task performance on the IGT (Glascher et al., 2012).

There were no significant group differences in performance, despite previous evidence of task impairments in paediatric ADHD and OCD (Garon et al., 2006; Kodaira et al., 2012). Owing to the focus on more sensitive neural outcomes, the current study may have been underpowered to detect significant group differences in performance, although both OCD and ADHD had a tendency to make fewer choices from the advantageous decks.

Limitations of the study include a lower IQ in the ADHD group, especially is there is some evidence linking IQ to modest but significant effects on IGT performance (Demaree, Burns, & DeDonno, 2010; Toplak, Sorge, Benoit, West, & Stanovich, 2010). However, lower IQ is typical for the population (Bridgett & Walker, 2006) and findings remained significant after covarying for IQ. Second, 50 % of patients were receiving psychostimulant medication which has been associated with increased fronto-striatal activation, suggesting that the deficit findings in ADHD in fronto-striatal systems may have been mitigated by their stimulant treatment, although all patients received a 48 hour wash out period, which is more than 10 times the half-life of the drug.

In summary, this is the first study to examine decision-making under ambiguity in paediatric ADHD and OCD using fMRI, as well as the first comparison of functional abnormalities during this task between ADHD and OCD patients. Findings of reduced VS activation during advantageous decisions and reduced neural sensitivity to wins and losses in MPFC and striatum in both ADHD and OCD patients are suggestive of shared impairments in outcome evaluation and learning signalling within mesolimbic regions responsible for updating reward representations on the basis of task feedback, that may underlie shared deficits in motivation

and decision-making in both disorders due to poor updating of expected outcomes associated with environmental stimuli and actions. Ventral MPFC was disorder-specifically underactivate in paediatric OCD relative to controls, in line with existing orbito-striatal accounts of the disorder, and extending findings of functional abnormalities in this region during sustained attention and TD in paediatric OCD from Chapters 6 and 7 to the domain of decision-making under ambiguity. Together, findings suggest potential shared neurocognitive underpinnings of decision-making abnormalities in ADHD and OCD, although vmOFC dysfunction is unique to OCD.

# Chapter 9. Overall discussion

## 9.1. Summary of PhD background and aims

ADHD and OCD are often comorbid and show similar performance deficits in a range of neuropsychological domains. Both disorders have deficits in inhibitory control, which are proposed to underlie problems with regulating impulsive behaviours in ADHD, and poor control over intrusive obsessive thoughts and compulsions in OCD (Barkley, 1997; Chamberlain et al., 2005; Robbins et al., 2012), as well as deficits in sustained attention, which in turn may underline poor concentration in ADHD, and difficulties disengaging from obsessional thoughts in OCD (Abramovitch et al., 2013; Clayton et al., 1999; Huang-Pollock et al., 2012; Losier et al., 1996; Mowinckel et al., 2015; Seli et al., 2016; Snyder et al., 2015; Willcutt et al., 2005). ADHD and OCD patients also show evidence of choice impulsivity and impairments in learning and utilising behaviour- and stimulus-outcome contingencies to guide goal-directed behaviour, with impulsive decision-making a key clinical feature of ADHD (Jackson & MacKillop, 2016; Noreika et al., 2013), while decision-making deficits in OCD may be manifested as a tendency to perform compulsive behaviours despite negative long-term consequences (Cavedini et al., 2002).

However, the two disorders are associated with very different symptom profiles (American Psychiatric Association, 2013), and ADHD is characterized by impulsivity, risk taking and hyperactivity while OCD patients are typically compulsive, risk averse and harm avoidant (Abramovitch, 2016; Abramovitch et al., 2012; Abramovitch, Dar, et al., 2015). Given their association with distinct symptom profiles in each disorder, it is possible that shared deficits in EF are mediated by disorder-specific patterns of dysfunction at the neural level. Therefore, the key question asked in this thesis is whether shared cool and hot EF performance deficits are associated with shared or disorder-specific neural underpinnings. Shared abnormalities

would suggest that shared cognitive deficits tap into similar underlying mechanisms in both disorders, whereas largely disorder-specific findings would suggest that shared performance deficits represent distinct phenocopies.

### 9.2. Basal ganglia in ADHD and OCD

The basal ganglia are consistently implicated in neurobiological models of ADHD and OCD (Cubillo et al., 2012; Menzies et al., 2008; Milad & Rauch, 2012; Rubia, Alegria, & Brinson, 2014). In the meta-analysis of adult and paediatric studies, patients with ADHD showed reliably decreased GMV in right caudate and putamen well as underactivation in these regions during inhibitory control. In direct contrast, patients with OCD show enhanced bilateral caudate and putamen GMV and disorder-specific overactivation in the posterior putamen during inhibitory control (Chapter 5), demonstrating disorder-contrasting differences in basal ganglia abnormalities in ADHD and OCD. Underactivation in right caudate was shared in the meta-analysis of inhibitory control tasks, as well as during the fMRI study of TD performance in paediatric ADHD and OCD (Chapter 7). During the IGT, shared VS underactivation during advantageous choices and putamen underactivation to wins was found in both disorders relative to controls (Chapter 8).

Findings therefore support that both disorders have abnormalities in basal ganglia structure and function. Importantly, however, the exact pattern of differences across tasks and modalities relative to controls is disorder-specific. The current findings support suggestions that underdeveloped and underactive basal ganglia are a feature of ADHD, with resultant impairments in salience detection, motivation and impulsivity (Aboitiz, Ossandón, Zamorano, Palma, & Carrasco, 2014; Volkow, Wang, Fowler, & Ding, 2005; Volkow et al., 2004; Volkow et al., 2009), but that OCD is associated with enhanced bottom-up influence of enlarged and functionally abnormal basal ganglia with resultant misattributions of

motivational salience to symptom provoking stimuli (Baioui et al., 2013; Banca et al., 2015; Mataix-Cols et al., 2004; Rotge et al., 2008; Schienle et al., 2005; Simon et al., 2014), as well as an imbalance between putamen-centred habit- and caudate-centred goal-directed networks in dorsal striatum (Banca et al., 2015; Gillan & Robbins, 2014).

Dopamine plays a key role in basal ganglia functioning (Dunovan & Verstynen, 2016; Keeler et al., 2014; Volkow et al., 2005; Volkow et al., 2004; Volkow et al., 2009), and dopaminergic abnormalities are closely implicated in ADHD and OCD (del Campo, Chamberlain, Sahakian, & Robbins, 2011; Dold et al., 2015; Gillan et al., 2016; Rubia, Alegria, Cubillo, et al., 2014; Schweren et al., 2015; Van Ameringen et al., 2014). Phasic dopaminergic responses are generated to rewards, and through dopaminergic dependent plasticity within the striatum, future action selection is biased towards behaviours which are associated with reward outcomes (Dunovan & Verstynen, 2016; Gillan et al., 2016; Keeler et al., 2014; Kollins & Adcock, 2014; Volkow et al., 2005; Volkow et al., 2004). Tonic striatal dopamine levels on the other hand modulate saliency, motivation, and emotional reactivity, and may also modulate learning rates and the balance between goal-directed and habitual behaviours (Dunovan & Verstynen, 2016; Gillan et al., 2016; Keeler et al., 2014; Kollins & Adcock, 2014; Volkow et al., 2005; Volkow et al., 2004). ADHD is proposed to be associated with reduced striatal dopamine, while OCD symptoms are proposed to result from a hyperactive dopaminergic system, with these hypotheses based on findings that ADHD can be treated with stimulant medications which increase striatal dopamine activity, whereas dopamine antagonists are effective augmentation medications in OCD (del Campo et al., 2011; Dold et al., 2015; Gillan et al., 2016; Rubia, Alegria, Cubillo, et al., 2014; Schweren et al., 2015; Van Ameringen et al., 2014). In ADHD, decreased dopaminergic functioning in the striatum may underlie deficits in motivation, task-related salience, reward-learning, and regulation of impulsive behaviours (Aboitiz et al., 2014; del Campo et al., 2011; Furukawa et

al., 2014; Tripp & Wickens, 2008; Tripp & Wickens, 2009; Volkow et al., 2005; Volkow et al., 2004; Volkow et al., 2009). In OCD, altered dopaminergic functioning is proposed to underlie increased bottom-up influence of symptom-provoking stimuli due to increased perceived salience and resultant compulsive behaviours (Denys, van der Wee, Janssen, De Geus, & Westenberg, 2004; Gillan et al., 2016; Nikolaus, Antke, Beu, & Muller, 2010). Findings of underactivation and reduced GMV in the basal ganglia are broadly in line with the notion of hypoactive dopaminergic functioning in ADHD, and enhanced GMV and increased putamen activation during inhibitory control tasks is broadly consistent with hyperactive dopaminergic functioning in OCD (Gillan & Robbins, 2014; Gillan et al., 2016; Keeler et al., 2014; Kollins & Adcock, 2014). Shared VS underactivation during a IGT task requiring responses to be made on the basis of reward learning suggests common impairments in phasic shifts of dopaminergic responses to stimuli and behaviour which predict reward (Chapter 8) (del Campo et al., 2011; Keeler et al., 2014; Kollins & Adcock, 2014; Tripp & Wickens, 2008; Tripp & Wickens, 2009). This might underlie shared tendencies to perform behaviours which do not align with positive outcome contingencies in the environment, such as impulsive behaviours in ADHD and compulsive behaviours in OCD, although given the above, the exact abnormalities in dopaminergic function and their influence on VS activity during the IGT are likely disorder-specific, and therefore a quantitative comparison between the two disorders on dopaminergic functioning is warranted.

The literature on the role of dopamine in ADHD and OCD has sometimes provided inconsistent findings often in small, comorbid and/or highly medicated samples (Fusar-Poli, Rubia, Rossi, Sartori, & Balottin, 2012; Nikolaus, Antke, Beu, & Muller, 2010). For instance, research in ADHD has shown both increased and decreased DAT levels, baseline D2/D3 receptor availability and stimulant-induced changes in D2/D3 receptor availability in patients

with ADHD relative to controls, while some studies report no differences between groups (Cherkasova et al., 2014; del Campo et al., 2013; Fusar-Poli et al., 2012; Spencer et al., 2013; Spencer et al., 2005; Volkow et al., 2007). In OCD, similarly inconsistent findings have been reported for studies of DAT levels (Hesse et al., 2005; Kim et al., 2003; Nikolaus, Antke, Beu, & Muller, 2010; van der Wee et al., 2004), although evidence points to reliably decreased D2 receptor availability (Denys et al., 2013; Denys, van der Wee, Janssen, De Geus, & Westenberg, 2004; Nikolaus et al., 2010; Perani et al., 2008). Reduced D2 receptor availability has been taken to support hypodopaminergic functioning in ADHD and hyperdopaminergic functioning in OCD, as decreased tracer binding may result from either a reduced number of D2/D3 receptors or due to increased competition from enhanced endogenous dopamine levels (Denys et al., 2013; Volkow et al., 2007). Nonetheless, meta-analytic evidence points to a role for exposure to stimulant medication in modulating DAT density in ADHD, with decreased striatal DAT levels reported in medication-naïve patients relative to controls, but increased levels reported in long-term medicated patients (Fusar-Poli et al., 2012), while in OCD DAT density may change from increased to decreased relative to controls over the course of illness (Nikolaus et al., 2010). Furthermore, the benchmark treatment for ADHD involves stimulant medications that increase striatal dopamine activity (Chan, Fogler, & Hammerness, 2016; Faraone, 2009; Faraone & Buitelaar, 2010; Van Ameringen et al., 2014), whereas dopamine antagonists are effective augmentation medications in OCD (Dold, Aigner, Lanzenberger, & Kasper, 2015). Future research could compare patients with ADHD and patients with OCD on biological markers of dopaminergic functioning. The patient samples should be sufficiently large to not only be able to detect group differences, but also to examine the effects of medication exposure, illness duration and symptom dimensions in each disorder on dopaminergic functioning. To further test striato-dopamine hypotheses of ADHD and OCD, research should examine the potential

relationship between dopaminergic functioning, GMV and activation in the striatum in each disorder. Finally, to examine the hypothesised disorder-specific mechanisms proposed to underlie shared findings of reduced D2 receptor availability in ADHD and OCD, research could also utilise a dopamine depletion paradigm to examine whether dopamine depletion is associated with greater increases D2 receptor availability (suggestive that baseline reductions in D2 availability are due to hyperdopaminergic functioning) in patients with OCD relative to patients with ADHD and controls (Abi-Dargham, van de Giessen, Slifstein, Kegeles, & Laruelle, 2009).

## 9.3. Prefrontal cortex in ADHD and OCD

### 9.3.1. Inferior frontal gyrus

Previous work points to the importance of IFG dysfunction in ADHD. This region has previously been found to be underactive in inhibitory control, attention, timing and decision-making tasks, to correlate with poor task performance and increased ADHD symptoms, and to be disorder-specific relative to OCD, bipolar disorder and conduct disorder (Cortese et al., 2012; Cubillo et al., 2010; Hart et al., 2012; Hart et al., 2013; Lei, Du, et al., 2015; McCarthy et al., 2014; Passarotti et al., 2010a, 2010b; Rubia, in press; Rubia, Cubillo, et al., 2010; Rubia, Halari, Christakou, et al., 2009; Rubia, Halari, et al., 2010; Rubia, Halari, Smith, et al., 2009; Rubia et al., 2008; Rubia et al., 2005; Vaidya et al., 2005; van Rooij, Hoekstra, et al., 2015).

The findings of this PhD support the importance of the IFG in ADHD. First, in a large meta-analysis, bilateral IFG was found to be disorder-specifically underactive relative to controls and patients with OCD during inhibitory control tasks, and dysfunction was reported in both paediatric (right side) and adult ADHD (bilateral) sub-group analyses (Chapter 5). These findings are in line with previous small studies comparing paediatric ADHD and OCD during

stop and switch tasks, which found disorder-specific right IFG underactivation in ADHD patients (Rubia, Cubillo, et al., 2010). In addition to previous comparisons with paediatric bipolar and conduct disorder, current findings support that IFG underactivation during inhibitory control may be a disorder-specific biomarker for ADHD relative to other childhood onset psychiatric disorders (Passarotti et al., 2010a, 2010b; Rubia, Halari, et al., 2010; Rubia, Halari, Smith, et al., 2009; Rubia et al., 2008). The IFG, particularly the pars opercularis sub-region in in the right hemisphere, is the hypothesised primary prefrontal region for inhibitory control, based on fMRI, lesion and TMS studies, with evidence pointing towards a direct role in initiating inhibitory control over inappropriate motor-responses through modulation of motor-cortex excitability via fronto-basal ganglia-motor cortex circuitry (Aron, 2011; Aron et al., 2004, 2014; Cai et al., 2014; Levy & Wagner, 2011). The current findings therefore support the notion that ADHD is associated with dysfunction within networks supporting inhibitory control (Barkley, 1997).

However, disorder-specificity was not reported across all tasks. In the sustained attention task, underactivation in dorsal IFG was disorder-specific in ADHD relative to OCD, while underactivation in ventral IFG was shared between disorders relative to controls (Chapter 6). During TD, underactivation in the IFG was shared between ADHD and OCD relative to controls (Chapter 7). The IFG is functionally heterogeneous, and forms part of numerous EF networks (Aron et al., 2004, 2014; Corbetta & Shulman, 2002; Hare et al., 2009; Noreika et al., 2013). Findings from this PhD are supportive of disruption in multiple IFG centred networks in ADHD beyond those implicated in inhibitory control, and including those involved in sustained attention and temporal foresight, in line with accounts proposing the IFG as the primary region of disruption in ADHD across EF domains (Rubia, in press; Rubia, Alegria, & Brinson, 2014). IFG deficits may be limited to specific EF contexts in paediatric OCD, with current findings suggesting IFG underactivation during TD and ventral IFG

underactivation during sustained attention. Disorder- specificity of IFG underactivation in paediatric ADHD has previously been shown relative to paediatric OCD during inhibitory control (Rubia, Cubillo, et al., 2010), but the current findings suggest that paediatric OCD is also associated with IFG deficits during other EF tasks and that therefore IFG underactivation as a disorder-specific biomarker for ADHD relative to OCD is task-specific.

Beyond its role in inhibitory control, the IFG is an important region in a hypothesised VAN involved in the detection of behaviourally relevant target stimuli (Corbetta & Shulman, 2002; Vossel, Geng, & Fink, 2014). Findings of shared ventral IFG/insula underactivation during sustained attention suggests that although disorders show disorder-specific DMN abnormalities in dACC in ADHD and in A/VMPFC in OCD, a failure to recruit VAN/SN IFG and insula regions may represent a common deficit which underlies deficits in shifting between DMN and task-positive networks in both disorders.

The role of lateral prefrontal cortex during TD is unclear, although degree of activation correlates with task performance, and disruption with TMS increases impulsive decision-making, supporting a role in effortful cognitive deliberation of options and making farsighted choices (Figner et al., 2010; Hare et al., 2014). Shared IFG underactivation suggests shared impairments in recruiting regions responsible for self-control in ADHD and OCD during TD that might ultimately underlie distinct symptomatology in each disorder, implying a transdiagnostic mechanism.

### 9.3.2. Medial prefrontal cortex

In OCD, medial prefrontal regions are most closely associated with the disorder (Radua & Mataix-Cols, 2009; Radua et al., 2010). In the multi-modal meta-analysis of adult and adolescent patients, patients with OCD showed overlapping reduction in r/d MPFC/ACC GMV and activation during inhibitory control that was disorder-specific relative to ADHD

(Chapter 5). These findings support the suggestion that OCD is associated hypofunctioning of a medial fronto-striato system supporting volitional goal-driven responding and inhibitory control (Gillan & Robbins, 2014; Gillan et al., 2016), and extend previous structural meta-analyses which report decreased GMV in the r/d MPFC/ACC (Eng, Sim, & Chen, 2015a; Goodkind et al., 2015; Peng et al., 2012; Radua et al., 2010) by showing for the first time that an overlapping region is also functionally abnormal during inhibitory control in OCD, and that structural and functional deficits in r/d MPFC/ACC are disorder-specific relative to ADHD. Previous meta-analyses have reported that decreased dorsal MPFC/ACC GMV is shared with affective, psychosis and addiction disorders (Goodkind et al., 2015; Radua et al., 2010). The current findings suggest that this common biomarker for psychiatric disorders is not shared with ADHD.

In the meta-analysis, both patient groups also showed decreased GMV in vmOFC (Chapter 5). However, in both the TD and IGT studies (Chapters 7 & 8), patients with OCD alone showed underactivation in vmOFC when making adaptive farsighted choices (i.e. delayed choices in the TD and advantageous choices in the IGT). Altered activation has also been reported during symptom provocation (Banca et al., 2015; Mataix-Cols et al., 2004), and a failure of vmOFC regulation over limbic and striatal functioning is proposed to underlie elevated anxiety and compulsivity in this patient group (Banca et al., 2015; Gillan & Robbins, 2014; Milad et al., 2013; Milad & Rauch, 2012). Findings point to the importance of vmOFC in hot EF in OCD, and suggest that alterations within orbito-striato networks may underlie a failure to regulate choices that have long-term negative consequences (e.g., engaging in compulsive behaviours) in favour of longsighted, goal-directed behaviour, perhaps due to poor integration with, or top-down control over, the basal ganglia (Banca et al., 2015; Gillan & Robbins, 2014; Gillan et al., 2016).

Aspects of medial prefrontal cortex also form parts of DMN and SN, and the interplay of these networks is important for maintaining external goal-directed attention (Menon, 2011; Menon & Uddin, 2010; Metin et al., 2015; Raichle, 2015; Raichle et al., 2001). During sustained attention, patients with OCD showed disorder-specific progressively decreasing activation in SN region the mACC with increasing delays. Both patient groups showed a failure to deactivate anterior DMN related activation, which in controls was progressively decreased with increasing delay. Patients with ADHD showed disorder-specific reduced deactivation in the dACC, while patients with OCD showed disorder-specific increasing A/VMPFC activation with increasing delays, thus showing that patterns of anterior DMN dysfunction were entirely disorder-specific during sustained attention.

The only shared functional abnormality in MPFC was reported in the IGT, wherein both patient groups showed reduced activation of the rostral MPFC to losses (Chapter 8). Reduced sensitivity to losses likely underlies continued impulsive and compulsive behaviours in ADHD and OCD despite negative outcomes. Reduced MPFC activation during feedback is line with previous work in adults with OCD (Becker et al., 2014; Figee et al., 2011), and previous studies in both adolescent and adult ADHD (Gonzalez-Gadea et al., 2016; Hauser et al., 2014), and consistent with accounts suggesting that ADHD and OCD patients have deficits using external feedback to learn new task rules (Nielen et al., 2009; Olley et al., 2007; Silvetti, Wiersema, Sonuga-Barke, & Verguts, 2013; Tripp, G. & Wickens, 2008; Tripp, Gail & Wickens, 2009).

To summarise, the patterns of MPFC abnormalities in GMV and function were largely disorder-specific between ADHD and OCD patients, and MPFC deficits were primarily associated with OCD, in particular in r/d MPFC/ACC during cool EF and vmOFC during hot EF tasks, although shared deficits in ADHD and OCD patients were found in vmOFC GMV and MPFC activation during loss processing.

### 9.4. EF and fronto-striatal in dysfunction in ADHD and OCD

The prefrontal cortex and basal ganglia operate together via parallel, functionally segregated neural networks to coordinate goal-directed behaviours, as part of so called fronto-striatal loops, and both ADHD and OCD have been classified as primarily fronto-striatal disorders (Cubillo et al., 2012; Fineberg et al., 2014; Marsh, Maia, & Peterson, 2009; Menzies et al., 2008; Robbins et al., 2012; Rubia, Alegria, & Brinson, 2014). The current findings have implications for models of fronto-striatal dysfunction in ADHD and OCD, namely that structural and functional abnormalities are largely disorder-specific and implicate distinct networks in each disorder. Overall, findings suggest that ADHD is associated with underfunctioning and underdevelopment in late developing lateral prefrontal and striatal regions responsible for EF (Shaw & Giambra, 1993; Shaw et al., 2014; Shaw et al., 2006; Shaw et al., 2013; Sripada, Kessler, & Angstadt, 2014), but that neuropathophysiology of OCD is characterized by structurally enlarged and functionally abnormal basal ganglia and structurally and functionally decreased MPFC (Melloni et al., 2012; Menzies et al., 2008; Milad & Rauch, 2012).

Performance on cool EF tasks appears to be associated with disorder-specific underlying dysfunction in ADHD and OCD, and disorders showed disorder-contrasting abnormalities in basal ganglia GMV, which was decreased in ADHD and increased in OCD. These findings are important for understanding the nature of the comorbidity between ADHD and OCD, and (Fineberg et al., 2014; Robbins et al., 2012). Heightened comorbidity between ADHD and OCD has been explained with reference to shared behavioural deficits in EF, which may tap into shared underlying neurocognitive mechanisms that could be expressed as either ADHD or OCD symptoms, perhaps depending on combinations with other disorder-specific neurocognitive mechanisms (Fineberg et al., 2014; Robbins et al., 2012). However, at least in the domain of inhibitory control and sustained attention, it appears that reported shared

performance deficits are associated with distinct underlying functional brain abnormalities, suggesting involvement of distinct underlying sub-processes, and indicating that shared performance deficits represent phenocopies rather than shared neurocognitive mechanisms in ADHD and OCD. Therefore, shared cognitive deficits in these domains are unlikely to explain heightened comorbidity between disorders, as deficits are not truly shared, and instead appear to reflect distinct underlying root abnormalities in each ADHD and OCD, presumably linked to distinct genetic underpinnings.

Interestingly, decision-making appeared to be associated with largely shared patterns of dysfunction in ADHD and OCD. This suggests that TD and IGT paradigms may in fact tap into neurocognitive mechanisms that are common to both disorders, namely striatal and rMPFC dysfunction during feedback processing and decision-making under ambiguity, and a failure to activate EF regions during TD. However, in line with orbito-striatal models of OCD, OFC underactivation was disorder-specific in OCD relative to controls and ADHD in both TD and IGT, suggesting that disorder-specific processes do also play a role in hot EF (Melloni et al., 2012; Menzies et al., 2008). Hot EF is understudied using fMRI in both disorders, and future research further elucidating shared and disorder-specific dysfunction during hot EF in ADHD and OCD is required.

These findings have important implications in light of recent movements, for instance the National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) research funding initiative, which propose moving away from conceptualization of psychiatric illness as a collection of categorically separate disorders (Insel et al., 2010). Instead, psychiatric illness is to be understood in terms of potentially transdiagnostic dimensions which cut across traditional diagnostic boundaries, and may be continuous in the normal population. Particular importance is paid to the idea of endophenotypes, commonly conceptualized as neurocognitive abnormalities which mechanistically underlie psychiatric symptoms,

potentially across disorders (Robbins et al., 2012). Treatment could then potentially be based on knowledge of a patient's profiles on sets of neurocognitive dimensions, rather than on a traditional categorical diagnosis (Insel et al., 2010; Lilienfeld & Treadway, 2016). Findings from the PhD highlight that studying potential shared endophenotypes, such as inhibitory control, sustained attention and decision-making, at multiple analysis levels is important for establishing whether deficits are truly shared, or instead merely surface similarities at the behavioural level. Findings suggest that similar cognitive deficits can have distinct biological underpinnings, and therefore categorising ADHD and OCD patients together on the basis of shared cognitive impairments in these domains is unlikely to be clinically useful, and treatments aimed at treating disorders by modifying these deficits are potentially unlikely to be successful across disorders, and may instead need to be based on disorder-specific knowledge of their underlying neurobiology.

### 9.5. Implications for future research

This PhD provides only the third study of shared and disorder-specific functional brain abnormalities in paediatric ADHD and OCD, with previously published work focusing on the domain of inhibitory control. This PhD therefore has numerous implications for future research.

As outlined in chapter one, ADHD and OCD are frequently comorbid, especially in paediatric populations. However, there are competing models of comorbidity. First, comorbid ADHD and OCD may represent true commodity, in which case both disorders are truly present in the same individual. Second, ADHD-like symptoms may result from "executive overload" in OCD patients. That is, OCD patients may show signs of impairments in attention, hyperactivity and impulsivity regulation as a result of cognitively taxing and physiologically arousing obsessive and compulsive symptoms (Abramovitch et al., 2012).

Alternatively, ADHD symptoms in OCD (and vice versa) may represent phenocopies with distinct underlying genetic and neuroanatomical bases, or else comorbid ADHD and OCD may be a distinct disorder with its own biological underpinnings (Geller et al., 2007a). Future work could therefore compare patients with ADHD, patients with OCD, patients with comorbid ADHD and OCD and healthy controls using structural and functional neuroimaging in order to inform models of ADHD and OCD comorbidity. This is especially interesting in light of findings in chapter 5 of disorder-contrasting GMV and activation abnormalities in the insula and basal ganglia, which is difficult to reconcile with a "true comorbidity" account of ADHD and OCD co-occurrence.

Future work may also investigate whether treatment methods are associated with the shared or disorder-specific changes in brain functioning in ADHD and OCD. For instance, a series of studies in adolescent ADHD patients investigated the acute effects of fluoxetine on functional abnormalities across a series of EF domains including response inhibition and TD, finding that fluoxetine normalised underactivation in right IFG during a Stop task and right IFG, insula, premotor cortex and striatum during the TD task (Carlisi et al., 2016; Chantiluke, Barrett, Giampietro, Santosh, et al., 2015). SSRIs including fluoxetine are first line treatment in OCD, and therefore it may be interesting to investigate whether right hemisphere fronto-insula-striatal regions respond similarly to pharmacological manipulation across disorders, or whether SSRI treatments instead act to normalise disorder-specific abnormalities, for instance in medial prefrontal cortex in OCD patients during these tasks.

Alternatively, recent novel experimental treatment methods including fMRI neurofeedback and transcranial direct current stimulation (tDCS) aim to treat symptoms by targeting specific brain regions. For instance, a recent study found that upregulating the right IFG using fMRI neurofeedback improved ADHD symptoms at an on average 11 month follow-up, and significantly enhanced right IFG activation post-training relative to pre-training during a Stop

task, and also reduced reaction time variability and improved sustained attention (Rubia et al., 2016). Similarly, targeting the right IFG with tDCS has been found to improve interference inhibition in ADHD patients (Breitling et al., 2016), and in OCD fMRI neurofeedback of anterior prefrontal cortex and vmOFC has been found to reduce contamination symptoms (Scheinost et al., 2014). Future work may therefore examine whether targeting particular brain regions has a similar effect on EF abilities and symptom improvement across disorders, or if targets need to be disorder-specific and based on knowledge of underlying differences in functional brain abnormalities between disorders.

Findings from this PhD of largely disorder-specific abnormalities also suggest that work utilising multivariate pattern analysis (MVPA) methods, which can be used to make individual predictions regarding class membership based on spatially distributed patterns of brain structure or activation, may be a useful endevour (Wolfers, Buitelaar, Beckmann, Franke, & Marquand, 2015). Even though the findings of this PhD suggest significant group differences in brain activation and GMV, univariate statistics are a poor tool for assisting diagnosis at the individual level, as there is typically substantial overlap across groups. Recent work in ADHD has used probabilistic classification models such as Gaussian Process Classifiers (GPCs), finding that is possible to accurately classify ADHD patients relative to controls and patients with autism based on GMV, as well as relative to controls during Stop temporal discrimination tasks (Hart, Chantiluke, et al., 2014; Hart, Marquand, et al., 2014; Lim et al., 2013), and a recent study accurately discriminated OCD patients from controls using GMV and WMV analysed with GPC methods (Hu et al., 2016). MVPA methods could be used to test the possibility of differentially diagnosing ADHD and OCD based on fronto-striatal activation and structure patterns. Furthermore, univariate analysis of neuroimaging data allows for elucidation of regions most involved in mediating task performance or which show broad, spatially extended differences in activation differences or structure between

groups. However, analysis of datasets in which ADHD and OCD show limited disorder-specificity when using univariate methods (e.g., the TD task) with MVPA could find differences in the patterns of activation across all voxels between patient groups, perhaps suggesting differences in underlying mechanisms at a finer-grained spatially distributed level.

### 9.6. Strengths and limitations of the study

The main strength of this PhD is that is provides the first direct comparison of paediatric ADHD and paediatric OCD during sustained attention and reward-related decision-making tasks using fMRI, finding evidence for shared and disorder-specific neural dysfunction. The PhD also includes a large meta-analysis, which for the first time elucidates regions with overlapping GMV and functional abnormalities during inhibitory control within ADHD and OCD, and provides the first meta-analytic comparison of GMV and functional abnormalities between the two disorders. The PhD focused on adolescent patients with ADHD and OCD. OCD remains under studied during adolescence, with the majority of previous fMRI studies in OCD having investigated adult samples. Finally, no previous published work has examined the neural abnormalities associated with sustained attention, TD or decision-making under ambiguity in OCD patients, or decision-making under ambiguity in adolescents with ADHD, and therefore this PhD provides an important initial investigation of the neural mechanisms that underlie performance on these tasks in these patient groups.

However, there are also limitations that could be addressed in future research. For instance, there were too few paediatric studies of inhibitory control in OCD patients for a sub-group analysis to be performed in the meta-analysis. Given that we found qualitative differences in GMV abnormalities in MPFC between adolescents and adults with OCD, which suggest maturational changes in associated underlying neural alterations, this means that the generalizability of the meta-analytic findings to paediatric OCD is limited. This further

highlights the need for more future research aimed at furthering understanding of the neural basis of paediatric OCD.

The significantly lower IQ in ADHD patients relative to controls and patient with OCD is a further limitation. Low IQ is reliably reported in ADHD, and may be considered part of the disorder (Bridgett & Walker, 2006). Covarying for differences between groups that were not randomly selected violates ANCOVA assumptions, as it is not possible to control for IQ differences between groups without removing part of the variance associated with ADHD (Evans & Anastasio, 1968; Miller & Chapman, 2001), and therefore IQ was not covaried in the first instance (Miller and Chapman 2001). However, supplementary analyses were performed which covaried for IQ to rule out that IQ was a confounding factor. In the SAT, all behavioural and neural findings remained the same after covarying for IQ. In the TD task, after controlling for IQ, the group differences in *k* remained significant at trend level ($p<.057$), and all fMRI findings remained except for activation in left superior/middle temporal/supramarginal gyrus/occipital lobe, which no longer differed significantly between groups. In the IGT, behavioural finding remained unchanged, and neural finings in vmOFC, VS and left putamen remained significant, and findings in SMA/PCC/precuneus, right putamen, precuneus and rMPFC remained significant at relaxed cluster thresholds. Therefore, although IQ was a potential cofound in this thesis, it did not alter the primary obtained results and conclusions.

While a strength of the current study is the largely medication naïve OCD sample (80%), the number of medication naïve patients differed across tasks in the ADHD group (SAT: 65%, TD: 46%, IGT: 50%). All ADHD patients received a 48 hour washout before completing the tasks. Subgroup analyses in the TD and SAT chapters showed that findings largely remained

significant in medication naïve patients, showing that group differences were not driven by exposure to different pharmacological medications in ADHD and OCD. Unfortunately, a similar analysis was unfeasible in the IGT chapter due to small number (n=8) of medication naïve ADHD patients. Moreover, the meta-analytic finding that, even post-washout, long-term treatment with stimulant medication is associated with increased activation in bilateral IFG suggests that potential group differences may have been reduced by stimulant exposure in this region (Chapter 5).

The fMRI studies included only right-handed boys, aged between 11-17. Previous work has shown an effect of handedness on brain laterality (Knecht et al., 2000), so including only right-handed participants isolated any potential laterality effects to differences in diagnosis, rather than differences in handedness. Differences in structural and functional brain development exist between males and females (Blakemore, 2012; Giedd & Rapoport, 2010; Paus et al., 2001; Rubia, 2013; Rubia, Hyde, Halari, Giampietro, & Smith, 2010; Rubia et al., 2013), and gender differences in brain structure and function abnormalities have been reported in ADHD (Onnink et al., 2014; Valera et al., 2010). Therefore, while including only boys increased homogeneity, it also means that findings are not generalizable to girls with ADHD or OCD. Due to maturational effects on brain development over the course of adolescence and early adulthood (Blakemore, 2012; Giedd & Rapoport, 2010; Paus et al., 2001; Rubia, 2013; Rubia, Hyde, et al., 2010; Rubia et al., 2013), findings are also not generalizable beyond paediatric patients, and future work should be conducted that compares adults with ADHD and OCD.

The OCD patient sample was too small to allow for examination of the effects of different OCD symptom dimensions on task performance and functional activation during cool and hot EF. This is an important limitation in light of previous findings of differences in

neuropychological performance and brain GMV and functioning between different symptom subgroups of OCD patients (Harrison et al., 2013; Mataix-Cols et al., 2004; McGuire et al., 2014; van den Heuvel et al., 2009), and this should be addressed in future research.

Sub-clinical depression and anxiety symptoms were not assessed and were likely higher in both patient groups relative to controls (McIntosh et al., 2009; Meyer et al., 2014). This is important in light of findings that depression and anxiety are associated with structural and functional alterations in fronto-striatal and fronto-limbic brain networks (Chantiluke et al., 2012; Norman, Lawrence, Iles, Benattayallah, & Karl, 2015; Radua et al, 2010; Remijnse et al., 2009; Remijnse et al., 2013; Wise et al., 2016). All participants were screened for clinical diagnoses of mood and anxiety disorders. Nonetheless, future work should covary or attempt to match for depression and anxiety symptoms across patient and control groups in ADHD and OCD research.

### 9.7. Final Conclusions and Final Remarks

In conclusion, this PhD has provided the first evidence of shared, disorder-specific and disorder-differential abnormalities in GMV and brain activation during inhibitory control in ADHD and OCD, as well as the first examination of overlapping structure-function abnormalities within each disorder using meta-analytic methods. Furthermore, this PhD provides the first comparison of paediatric ADHD and OCD patients using fMRI using sustained attention and reward related decision-making tasks.

Structurally, ADHD and OCD showed opposing GMV abnormalities in overlapping regions of the basal ganglia, which were enlarged in OCD and decreased in ADHD relative to controls, and OCD patients showed disorder-specific decreases in r/d MPFC/ACC GMV. In cool EF tasks, functional deficits were largely disorder-specific. In particular, in ADHD,

underactivation in bilateral IFG was disorder-specific during inhibitory control, in line with previous studies comparing ADHD and OCD, and DLPFC/dorsal IFG sub-region was disorder-specific during sustained attention, while OCD was associated with disorder-specific dorsomedial prefrontal underactivation. Shared overactivation was seen in the posterior DMN, but in the anterior DMN ADHD patients showed enhanced dACC activation while OCD patients showed disorder-specific increasing activation with increasing delays in A/VMPFC. These findings suggest that behavioural deficits in these domains are phenocopies with distinct underlying neural mechanisms. During "hot EF" reward-related decision-making tasks, patients with OCD alone showed underactivation in vmOFC, in line with orbito-striatal accounts of OCD. However, there was evidence of shared neural underactivation during TD in right sided fronto-insula-striatal network implicated in self-control and temporal foresight, suggesting that choice impulsivity in ADHD and OCD may be associated with partially overlapping neural underpinnngs. Shared deficits in the VS during IGT are in line with previous findings of VS underactivation in both disorders, and suggests shared deficits in linking anticipatory mesolimbic dopaminergic firing to stimuli that predict rewards. Overall, results show that ADHD and OCD are associated with largely disorder-specific structural and functional alterations in fronto-striatal and DMN networks, suggesting that shared behavioural impairments are primarily associated with distinct mechanisms at the underlying neural level.

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